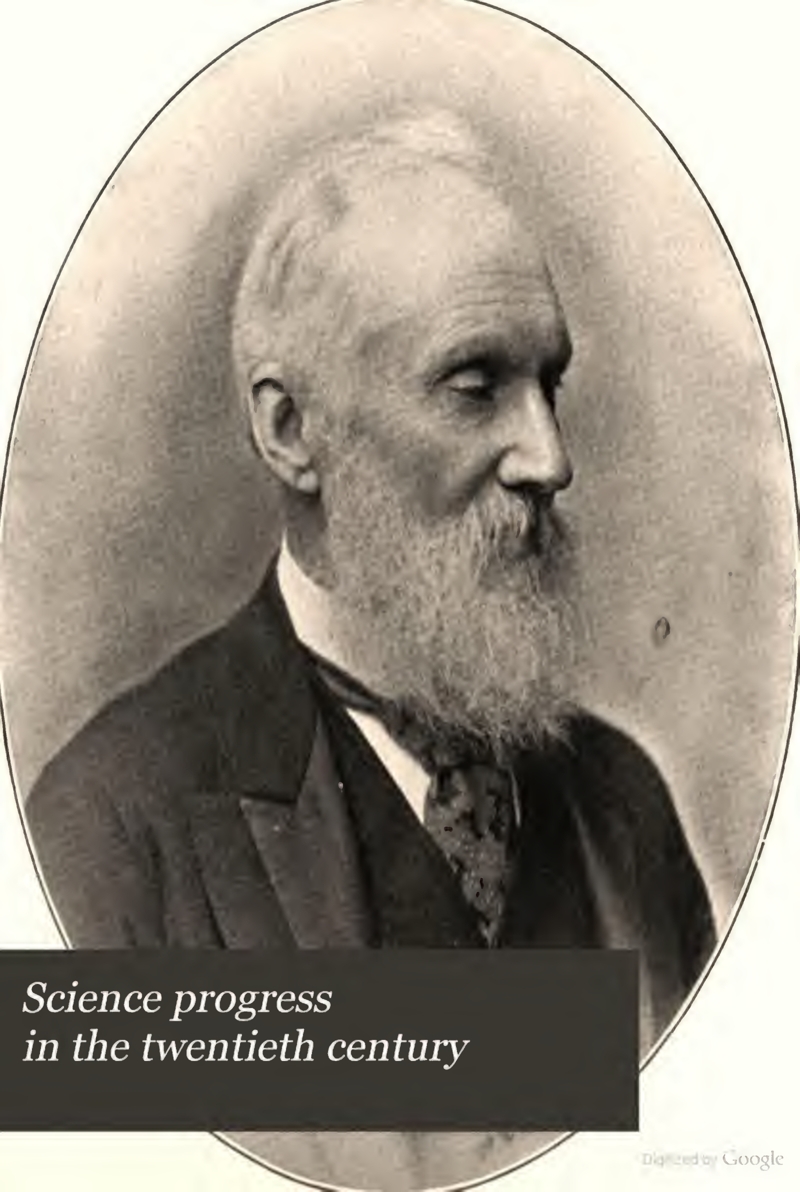

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ERRATA.

THE SEQUENCE OF PLANT REMAINS IN THE BRITISH PEAT MOSSES.

Owing to the author's absence abroad, and the proofs not reaching him until after publication, several misprints occur in the text.

The following are the chief errata :—

Page 318, line 32, for *plot*, read *foot*.
,, 320, ,, 21, ,, *Bycopus*, read *Lycopus*.
,, 321, ,, 12, ,, *Stellaria media*, read *Chrysanthemum Segetum*.

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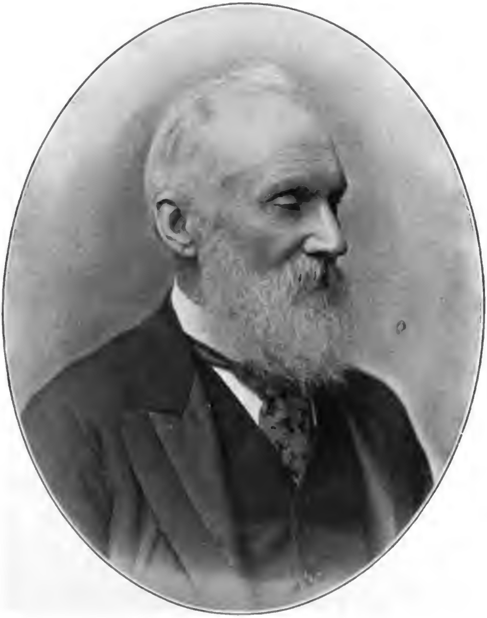

Kelvin
Feb 11, 1904

WILLIAM THOMSON

BARON KELVIN OF LARGS

P.C., O.M., G.C.V.O., F.R.S., F.R.S.E., LL.D., D.C.L.

BORN JUNE 26, 1824; DIED DECEMBER 17, 1907
BURIED IN WESTMINSTER ABBEY

ON the death of Lord Kelvin there passed away one who will always remain identified with the remarkable progress achieved by science during the nineteenth century. At the celebration, in June 1896, in honour of the jubilee of his professorship at Glasgow, Lord Kelvin referred to his original contributions to science "as a record of persevering endeavour to see below the surface of matter." This endeavour resulted in profoundly modifying some of the conditions of life for many of the inhabitants of this world, in virtue of his extraordinary faculty of applying to practical matters the fruits of his researches. In this connection it is not necessary to do more than refer to the great part he played in the development of submarine telegraphy, in the improvements he effected in the sounding plummet and the mariner's compass, in the invention of accurate and sensitive instruments for electrical measurements, and in the general advancement of electrical engineering. His researches on the tides added greatly to our knowledge, both theoretical and practical, of these important phenomena, and furnished another line of attack on the problem of solving the age of this earth.

In pure science, by his researches in thermodynamics, wave motion and vortex motion, Lord Kelvin advanced greatly human knowledge of the properties of matter. The whole civilised world recognised him as one of the most brilliant natural philosophers of all time, and now mourns his loss.

THE PHOTOGRAPHY OF COLOUR

By CHAPMAN JONES, F.I.C., F.C.S., etc.
Royal College of Science, London

I

As this problem has engaged the attention of innumerable workers for nearly a hundred years, and the best methods so far known are now carried out on a considerable scale, it is obviously impossible to deal with the subject with any approach to completeness within the compass of an article such as this. I propose, therefore, to consider the principles involved rather than the practical details, and to deal with the subject broadly rather than minutely.

It is worth while first to ask, What is meant by the expression "photography of colour"? There is no doubt whatever as to what it means in its simplest conception. Ordinary photography depicts form with an accuracy and minuteness that far exceeds the best handwork; and by special care—that is, the use of special lenses and of cameras made after the manner of surveying instruments—it is possible to get results that may be depended upon for surveying purposes. Not only is correct "drawing" inherent in photography, but also the rendering of light and shade—that is, the comparative luminosities of the various parts of the object, within certain limits that are well understood. The simplest idea and the most acceptable method of the photography of colour is that in which the colour of the object is reproduced as automatically and correctly as its shape, and shall be visible on ordinary inspection as the colours of a painting are. Such colour photography has been eagerly sought for but is as yet impossible; and if one is justified in judging of the future in the light of the past, it will remain impossible. There does not seem any line of work that can lead to such a result. From this point of view colour photography as now practised is always a compromise.

The methods of both the past and the present naturally fall into two great classes, or, more correctly perhaps, a greater class and a lesser class. The less important division includes methods in which a single homogeneous surface is employed, while in the larger division the surface is multiple or non-homogeneous. The first is generally an attempt to get as near as possible to the simple colour photography described above, while the second is entirely indirect in that it does not aim at producing colour at all, but only at automatically locating suitable dyes or inks. We will consider the direct method first.

Dr. T. J. Seebeck, of Jena, in the year 1810 or thereabouts, while making some experiments as to the action of the solar spectrum on silver chloride, observed that the violet light of the spectrum produced a reddish brown substance sometimes inclining towards violet, that the blue light produced a blue substance, and the red a rose or lilac substance. If the silver salt had previously been exposed to light for a time, so as to darken it, there was a bleaching action where the red and yellow light fell upon it. It is hardly likely that he had in mind any photographic process whether in colour or otherwise, as photography at this time was not a practical art. Eight years before this Sir Humphry Davy had described at the Royal Institution the attempts of Thomas Wedgwood, which he had supplemented, to get a practical photographic method—a printing process as we should now call it—but their preparations were very lacking in sensitiveness, and no method of fixing them was known. Of those who were primarily concerned in working out practical photographic methods, the elder Niepce began his work in 1814, Daguerre in 1824, and Fox Talbot in 1833, and it was not until 1839 that their work culminated in serviceable processes.

Edmund Becquerel appears to have been the first to specifically attack the problem of the photography of colour. It is stated that he began his investigations in 1838, though he did not publish any results of them until ten years later. Although the earlier date was just before the methods of Daguerre and Talbot were published, there is no doubt that there was a general knowledge in scientific circles that something of the kind would shortly be made known, and that this directed the attention of many investigators to the possibilities of photography. But long before 1848 other workers had made observations concerning the photography of colour. Sir John

Herschel had repeated Seebeck's experiment; Daguerre and Fox Talbot had both observed that in some of their photographs a red object produced a red colour in the picture; and Robert Hunt had succeeded in obtaining colours on paper impregnated with various silver salts. Hunt put, for example, a prepared sheet under red, yellow, green, and blue glasses, and exposed the arrangement for a week to diffused light. The silver chloride "became red under the red glass, dirty yellow under the yellow glass, a dark green under the green, and a light olive under the blue." But with a sheet "differently prepared" he tells us he obtained "a very beautiful picture," in which the sky was crimson, stucco-fronted houses came out slaty blue, and the green fields of a brick-red tint.

Becquerel used silver plates and produced a layer of silver chloride on the surface of the metal, at first by the action of cupric chloride, but afterwards by the electrolysis of dilute hydrochloric acid with the silver plate as the positive electrode. The plates were treated until the very thin layer of the accumulating chloride on their surfaces had passed through certain definite colour-changes, and then washed, dried, and warmed. With these plates he reproduced, with a considerable measure of success, the colours of brightly dressed dolls and highly coloured designs besides the solar and electric arc spectra.

There were many others who busied themselves with experiments of this character at this time and for many years afterwards, making little variations and meeting with more or less success, sometimes propounding strange theories and endeavouring to justify them, and now and again expressing their hopes and almost their convictions that what they sought for was just coming within their reach. But their hopes were ill founded, for the work was purely empirical; they had no sound principles to guide them, and no real progress was ever made. Even the colours obtained were not permanent, and though some when considerable care was taken to preserve them lasted longer than others, the difficulty of "fixing" them, or rendering them even moderately stable, was never overcome. We shall shortly see something of the nature of the colours produced in these experiments.

If light waves are similar to the waves produced by disturbing the surface of water, as they are supposed to be, it follows that if a continuous series of waves is reflected back upon its original path, the waves travelling in opposite directions will interfere with each other. It is clear that as they move in opposite directions each wave will alternately coincide with and oppose a wave of the series that it is meeting, and that where they coincide their moving power on the particle concerned will be added, and that where they are opposed the particle can obey neither impulse, and therefore remains stationary. There is thus produced a series of "standing waves," for although their crests rise and fall or move to and fro at (practically) right angles to the path of the disturbance, they move in neither direction along the path. The alternate crests move in opposite directions, and between each and the next there is a stationary point. If these conditions are realised in light waves, the light will be quenched at those points where the movement of the particles (of the luminiferous ether) is prevented, and there will result a series of layers of light with intervals of darkness half a wave length apart.

Dr. W. Zenker, of Berlin, in 1868 published a small volume, *Lehrbuch der Photochromie* (*Photographie in natürlichen Farben*), in which he examined in detail the methods, theories, and results of the work that had been done up to then in connection with the reproduction of colour. While satisfied that coloured light will under certain conditions produce something that reflects the same, or very nearly the same, colour as the incident light, he points out the insufficiency of the theories of the change that had been put forward. The colour of the incident light, though reproduced more or less in all cases, is especially noticeable when silver plates are used, as in the method of Becquerel. He then explains the nature of standing waves, and advances this as an explanation of the phenomenon. The silver chloride, especially if violet (that is, slightly reduced), is so affected by the light that metallic silver is produced in layers, with intervals of no chemical change which correspond to the parts where the light is quenched by interference. He supposed metallic silver to be produced because it is necessary for the reproduction of the colour that the product of the change shall be a good reflector. As to why reflecting laminæ of this kind should reflect only or chiefly light of the same wave length (or colour) as the light which produced the laminæ when they are illuminated by white light, he explains that light of a greater or less wave length than that of the original incident ray will be out of harmony with the reflecting laminæ, so that the reflections from the various laminæ will be in dissimilar phases, and the resulting interference will cause this light to be more or less extinguished. But that part of the white light that corresponds in wave length to the original ray will be reflected at each lamina in such a manner that the difference in progression will always be equal to exactly a whole wave length, and therefore the light reflected from each surface will reinforce that from every other. He considered that this explanation followed from the wave theory of light, and required only one hypothesis, namely, that the product of the light action should reflect light strongly.

Although Zenker was not entirely correct and his theory did not pass unchallenged, his work eventually proved to be of great importance. Still, it was hardly appreciated at the time, and was apparently soon forgotten. Perhaps the method of its publication militated against its being widely known.

Lord Raleigh in 1887, and Prof. Otto Wiener of Aachen a few years later, both independently and without knowledge of Zenker's work, suggested that the production of standing waves might account for at least some of the results of the early colour photographs. But Wiener went a great deal further than this, and in 1895 published the results of an exhaustive examination of these methods, including the testing of pictures produced by them, to determine whether the colours were due to pigmentary matter or interference or both. He used a right-angled prism of dense glass with its three faces polished, placing the hypothenuse surface in contact with the spectrum photograph to be tested, with a liquid of high refractivity (benzene) between to exclude air, so that the refracting edge of the prism crossed the colour boundary. The colour was then viewed, with certain precautions, so that part of it was seen directly and part through the prism. With a pigmentary colour both parts remained of the same tint, but a colour due to interference was changed by the presence of the prism, so that, for example, yellow appeared bluish green. Wiener prepared some examples by Seebeck's method (precipitated silver chloride darkened by exposure to white light and then exposed to the spectrum), and found the red a rose-red, the blue greyish, and the green and yellow very poorly represented, if at all. He found these colours to be pigmentary. A modification, due originally to

Poitevin, but with slight improvements, was investigated. Silver chloride precipitated in paper was exposed to daylight in a solution of stannous chloride until darkened. It was then immersed in a solution containing potassium bichromate and cupric sulphate and exposed slightly moist. This reproduces all the colours more or less, but with a tendency towards a yellowish brown tint. These colours also are pigmentary. The colours produced by Becquerel's process, in which a silver plate has its surface converted into chloride by the electrolytic method, were found to be chiefly interference colours due to the action of standing waves, but there was pigmentary matter also present.

The colour obtained in these older processes being due entirely to pigmentary matter, except when a metal plate was used, the natural question is, What is the character of the pigmentary substance? Wiener found that silver subchloride was sensitive to all the colours of the spectrum as silver chloride that has been exposed to light is, and as these two substances are alike in other properties, there seems little doubt that silver subchloride is the colour-sensitive substance in these processes. Why it should be changed by coloured light into a substance that has some approach to the colour of the light that falls upon it is a problem still unsolved. But it seems exceedingly unlikely that any useful method of colour photography will be realised on this line of work, because the colours at their best are only approximately similar to the colour of the light that produces them; they cannot be fixed because the pigmentary matter is decomposed by solvents of silver chloride; the subchloride does not bleach to white in white light, nor is it itself black—two conditions that must be fulfilled in a material that is to reproduce colours by the direct action of light. Wiener suggested as the ideal material a black mixture of three differently coloured substances which are bleached to white by white light, and are sensitive in proportion to their absorption. In the next section the practical realisation of this principle will be described.

We have already seen that "standing waves" were predicted as a necessary result of the undulatory nature of light, and it appears that several physicists sought to obtain experimental evidence of their existence, but it was not until 1891 that Prof. Gabriel Lippmann of Paris was successful. If these standing waves could be produced in a photographic film, it was argued that deposits of silver should be obtained starting where the amplitude of vibration is greatest, with no deposit at the nodes, and that these layers would reproduce the colours that originated them when they were illuminated with white light and viewed under suitable conditions. This, therefore, would constitute a method of colour photography. It is obvious that for success the film used must be sensitive to all colours, it must have a good reflecting surface to send back the incident light, it must be transparent so that the reflected light may be as nearly as possible of its original intensity and that there may be a negligible amount of scattered light in it, and the sensitive material must be grainless, or very nearly so, for the layers of silver to be produced would be distant from each other, centre to centre, a dimension equal to only half a wave length of the light producing them. Lippmann solved the problem by coating glass with a suitable emulsion, and exposing it in a dark slide constructed to hold mercury. The glass side of the plate was turned to the light, and the sensitive film was backed up by the mercury which formed the reflecting surface. The evidence of his success lay in the facts that there was an obvious absence of pigmentary matter, the deposit being only grey silver, but that the colours of the original were reproduced as theory indicated by proper illumination and inspection, and that the colours changed by treating the film in any way that would alter the distance between the layers of silver, as, for example, by breathing on the plate and so slightly expanding the film. Perhaps the chief difficulty of this method is in ensuring that when finished the film shall be in exactly the same condition as during the exposure, or at least that the distances between the silver deposits in the finished plate shall exactly correspond with the distances between the nodes of the standing waves of the incident light. The chief drawback to the results is that they must be illuminated and viewed at suitable angles. Many workers improved the process in details, and some very excellent results have been obtained.

It still remained to actually demonstrate the existence of the laminæ of silver in the film. Dr. R. Neuhauss, Mr. E. Senior, and others afterwards, cut transverse sections of Lippmann films and obtained distinct proof of the presence of the laminæ, but by far the most complete and successful investigation of these films has been published quite recently by Prof. S. R. Cajal of Madrid. As the resolution of the laminæ requires an objective of a numerical aperture equal to or greater than the greatest available, Cajal swelled his sections in water and so obtained excellent definition. He has photographed sections of all kinds, and analysed the effects by such methods as rubbing away the surface to distinguish between the effects of the superficial and the underlying parts. He confirms Zenker's theory exactly, except, perhaps, with regard to white. This he found was not due to the production and mixing of all colours or even complementary colours, but to simple reflection from a superficial deposit of silver; and in tinted whites or light colours he also found this superficial layer, but here it is partly transparent, and the interference colours produced by the laminæ below show through it.

Although attempts have been made, up to quite recently, to perfect the methods in which silver subchloride is the sensitive material, Lippmann's process may be regarded as the final result of all attempts to photograph colour directly. It is an exceedingly beautiful process to the experimentalist, but it has so many possibilities of error that it is very uncertain, and therefore unsuitable for general purposes as a method of photography in colours.

II

The Young-Helmholtz theory of colour vision supposes that the normal human eye is sensitive to only three fundamental colours; that is, that the points of sensitiveness of the retina, whatever they may be, are of three kinds. When white light falls upon the retina all three are excited to a definite (or equal) proportion, and when this proportion of excitation varies we become conscious of colour. Granting this, it follows that if the colour can be found that corresponds to each kind of sensitiveness, we shall have three colours that will, by their mixture, serve to imitate every possible colour, including, of course, black and white. These three fundamental colours have been determined from time to time by various investigators, and may be roughly described as red, green, and blue. We may then, for reproduction purposes, regard the light reflected from any object whatever, when illuminated in any manner whatever, as consisting of a mixture of these three colours (or two or one of them), and by restricting the light that falls upon a sensitive plate to one of them at a time, a photograph can be made of each light-constituent reflected by the object. The photographs are themselves colourless, but they are colour records, and it only remains to bring together the three colours as indicated by the photographs to produce a picture that appears of exactly the same colours as the original—because it has exactly the same effect upon the retina. In this case no colour is produced by photography or by the photograph: the colours are pigments or dyes, and the photography merely locates them.

This is the principle of "three-colour" processes, and, speaking practically, all indirect colour photography comes under this description. It must not be thought that three-colour work is dependent upon the Young-Helmholtz theory of colour perception—it is founded rather upon the experimental facts that underlie that theory. The theory and three-colour processes are better regarded as two independent products of the same set of facts, and these facts will remain whatever fate awaits the colour-vision theory. Indeed the connection between this theory and three-colour photography may not be so intimate as it appears to some to be. The colours that represent the three sensations are fairly definite, and Colonel von Hübl maintains that the number of sets of three colours that will serve for three-colour work is indefinite. He arranges the spectrum tints in a circle with complementary colours diametrically opposite each other on a plan that would take too long to describe here, and states that the best three colours will be at the angles of an equilateral triangle drawn in the circle, and that the triangle may be in any position. At the same time he allows that practical considerations—chiefly the difficulty of getting a bright yellow by the mixing of pigments—obliges one to use the three colours which, if they do not exactly match the three primary sensation colours, approximate to them. Sir William Abney, who has done a great deal of work in this connection, and is a very successful producer of colour photographs, accepts absolutely the Young-Helmholtz theory of colour vision as his guide, and has redetermined the spectrum curves of the primary sensations. Mr. F. E. Ives, who has worked as a pioneer with very notable success in many departments of colour photography, does practically the same, working according to Maxwell's curves. On the other hand it has been stated that the colour screens used by various workers do not always conform to their theories. It must be borne in mind, however, that the dyes and pigments used have to be selected from those that are available, and that the best of them are only more or less close approximations to what is really sought for. Thus the theories as to the selection of the colours are more diverse than the practice.

Having obtained the red, green, and blue records, there are two distinct methods by which the colours may be combined to form the picture. Each may be caused to give its appropriate colour separately, as by the use of a set of three optical lanterns, each giving one of the required colours (the photograph regulating its distribution and intensity), the three coloured images being superposed on the screen. The three colours are added together, light is added to light; the combined effect of all three is white and their absence is black. In the other method the three colour prints are superposed to form a single print or transparency. Here the combined effect of all three is black, their absence is white, and each colour subtracts whatever it can from the light—the same light that passes through all of them. In the first case the lights are added, and in the second the absorptions. The first is sometimes called the additive method and the second the subtractive method. The colours transmitted by each of the three prints in the second method must be the complementaries of those transmitted in the first case. Taking for example a red patch in the original, this will give a transparent or depositless place on the print that represents the redness of the original, which, by the triple lantern method, would give a red patch on the screen as required. But for printing or staining purposes this holds no colour, and so remains colourless. The prints that represent the greenness and the blueness of the original will be coloured at this part, the former by a colour that absorbs green and transmits red and blue, the latter by a colour that absorbs blue and transmits red and green. Thus the only colour that can get through the three superposed coloured images is the red, as required. In the additive method each image contributes one of the three colours, in the subtractive method each image subtracts or absorbs one of the three colours. These are the general principles of three-colour photography in its two main sections.

Three-colour photography is practised commercially on a very large scale, and has been investigated and discoursed upon by a vast number of persons. A great many have dealt with the subject from a purely scientific point of view, while printers, ink-makers, and others look only at practical results. I propose therefore only to indicate the chief facts concerning its development, and to consider the most important processes that are in use at the present.

It seems that Clerk Maxwell was the first, in 1855, to suggest the principle of three-colour photography, but he used it as an illustration of the functions of the three systems of nerves according to Young's theory rather than a suggestion for practical photography. He says: "Let a plate of red glass be placed before the camera and an impression taken. The positive of this will be transparent wherever the red light has been abundant in the landscape and opaque where it has been wanting. Let it now be put in a magic lantern along with the red glass, and a red picture will be thrown on the screen. Let this operation be repeated with a green and a violet glass, and by means of three magic lanterns let the three images be superimposed on the screen . . . a complete copy of the landscape, as far as visible colour is concerned, will be thrown on the screen. The only apparent difference will be that the copy will be more subdued or less pure in tint than the original." Then he goes on to consider the eye in connection with colour vision. At the Royal Institution in 1861, Clerk Maxwell showed the experiment, using tanks of coloured liquids instead of coloured glasses, and showed the photograph of a coloured ribbon with three magic lanterns; but of course the colours were deficient because it was almost impossible at that time to photograph by red or green light.

Within the next few years others engaged themselves with the subject, but the most notable worker was Louis Ducos du Hauron, who, in 1869, published a small volume, entitled *Les Couleurs en Photographie: Solution du Problem.* He described the triple lantern "additive" method; a method of combining the three coloured images by means of mirrors; the production of prints by superposition of the coloured images—the "subtractive" method and a single-plate method—the three colours being arranged in fine lines or otherwise on one plate. In the same year he showed some results at a meeting of the Société Française de Photographie. By a curious coincidence, at the same meeting, Charles Cros entered into great detail as to the various possible methods of trichromatic photography. But Cros appears to have contented himself with suggesting how others might succeed, while Du Hauron put his notions to the test of experiment. Moreover, it appears that Cros was wrong in his colours, recommending pale tints of red, yellow, and blue for the screens for getting the three negatives.

Work of this kind was very difficult because of the insensitiveness of the collodion plates then employed to green and especially to red light. It was not until 1873 that the sensitising effect of certain dyes upon photographic plates was discovered by Prof. H. W. Vogel. Now by this means plates can be made usefully sensitive even into the infra-red. The possibilities of special sensitising, and the introduction of gelatine dry plates about 1878, cleared away many difficulties that sorely hampered and might well have discouraged the earlier workers. From this time the development of three-colour photography was a matter of perfecting details rather than evolving new principles, and devising methods for converting laboratory experiments into commercial methods.

The additive method—the three coloured images being separately illuminated—was made into a really practical method by Mr. F. E. Ives, of Philadelphia. Mr. Ives first exhibited his apparatus in London in 1892, but four years before this he had demonstrated the capabilities of the process at the Franklin Institute in Philadelphia. In 1893 his "photo-chromoscope," afterwards called "Krōmskōp," was on the market. The apparatus that he devised for the purpose consisted of a camera for taking the three colour records, a triple lantern for projecting the picture on to the screen, and the photo-chromoscope. This last is a compact apparatus containing three coloured glasses, one for each colour record as required, and a system of mirrors, so that the three coloured images are seen superposed by looking in at the eye-piece. Shortly afterwards the apparatus was made stereoscopic. The reproductions as seen in this apparatus are remarkably realistic, and I do not think that any method has surpassed them. The one drawback is that an apparatus has to be used for seeing the pictures. Mr. Ives says that he worked "in accordance with the Young-Helmholtz-Maxwell theory of colour vision." "Although the three fundamental colour sensations are red, green, and blue-violet, the three images of the triple photograph are not made through red, green, and blue-violet glasses, nor by the action of red, green, and blue-violet rays, but each by the joint action of all rays that have power to excite the respective fundamental colour sensations, . . . according to the measurements of Maxwell and Abney." Thus the colour screens used for taking the object each transmitted a large proportion of the spectrum. But for viewing or projecting the photographs Mr. Ives claimed to use colour screens that transmit only a narrow band of the spectrum, just that part in each case that will best excite the one sensation, and, as far as possible, that only. The disadvantage of narrow-band colour screens is that they transmit comparatively little light, and it has been stated that the screens used by Mr. Ives did not well conform to his theory. I have already referred to the uncertainty of these matters, but assuredly Mr. Ives was guided by the principles he professed, and he was remarkably successful.

The necessity for taking three separate negatives is obviously a circumstance to be avoided if possible, and the method of avoiding it was pointed out by Du Hauron in 1869. It appears that the only practicable method of making one plate suffice is to divide the surface of the plate among the three colours, using such small parts of the plate for each that when viewed in the usual way these parts merge into each other, as the fine detail of the impression of a copper or steel engraving does. The drawback to all such methods is the great loss of light. If any colour is represented by only one-third the area of the patch that stands for it, the area which might otherwise be all colour is two-thirds black. Thus two-thirds, more or less, of the light that would form the image in Ives' apparatus is lost in a one-plate process, and the picture is correspondingly duller unless the light is proportionately increased. This can be accomplished if the picture is in the form of a lantern slide, by using the same light in the lantern but reducing the diameter of the picture on the screen from 10 ft. to 6 ft. or less, or from 8 ft. to something under 5 ft.

The first successful methods of this kind were worked out independently by Dr. John Joly, of Dublin, and Mr. J. W.

McDonough, in America, from 1892 to about 1898. The later years of this period include attempts to make the process workable, so that the screens necessary might be manufactured in quantity, but in this they were not successful. The three colours were arranged regularly in lines, and were applied to the glass by means of a ruling pen, though other methods were tried afterwards. Dr. Joly followed Ives very nearly so far as his colours were concerned, except that he sought to get his colours to accord with the more recently determined sensation curves. He used two colour screens—a "taking screen" that was fixed in front of the plate while the exposure was being made, and a "viewing screen" which was put in front of the positive for seeing the picture, and might be bound up with it as a fixture if preferred. The lines were always so coarse as to be obtrusive.

Quite recently, after years of work, Mr. John H. Powrie, of Chicago, assisted by Miss Florence Warner, has so far perfected a triple-line method that he has been able to show many excellent examples. He has overcome the difficulty of making the fine coloured lines by discarding ruling methods altogether. He coats the glass with a suitable colloid made sensitive with potassium bichromate, and exposes this to light under a black-line screen that has lines twice the width of the spaces between them. The light makes the colloid insoluble in warm water, so that when "developed" like a carbon print, the coating is entirely dissolved away where it was protected by the black lines of the screen, and remains on the glass in fine lines corresponding to the screen spaces. The plate is put into a solution of a green dye; the colloid absorbs the dye, and thus the green lines are formed. The colloid is made quite insoluble to fix the dye. The plate is then coated again, and treated exactly as before; but care is taken that the black lines of the screen hide the green lines already produced, and a red dye is used. It remains to get the blue lines that shall exactly fill the spaces between the two sets of lines already obtained and without any overlapping of them. The plate is coated again, and this time exposed to light without the black line screen, but with its back to the light, so that the red and green lines on the plate prevent any light effect on the coating that overlies them and acts only upon the parts between. Warm water dissolves away the new colloid layer over the green and red lines, leaving it exactly filling the spaces between them. The plate is put into a solution of a blue dye to stain the new lines. By this method the lines can be made more than twice as fine as by ruling (more than 600 to the inch), and the troubles of overlapping and of uncoloured gaps are entirely obviated. The method of using these plates, when they are issued to the public, will doubtless be similar to that of the Lumière "Autochrome" plates, described in the next paragraph. Their special advantages will be referred to later.

It may be here mentioned in passing that during the last twelve years it has been shown by many workers to be possible to get three colours that will serve more or less well by the use of prisms or diffraction gratings instead of dyes or pigments. But these methods do not appear to lend themselves kindly to practical work, even if no exception is taken to the principles upon which they are based.

Instead of arranging the three colours in lines, they may be disposed in small hexagon or square patches. These methods have been patented, but nothing practical has yet come of the idea. The third alternative is a random grain, and a method of doing this by means of starch granules, which was described by Messrs. Lumière, of Lyons, rather more than three years ago, has just been commercially perfected. Quantities of starch granules of approximately uniform size are stained respectively red, green, and blue, mixed as thoroughly as can be in such proportions as present a neutral grey to the eye, and dusted over a prepared plate so that they adhere in a single layer, which is then pressed or dusted with a black powder (or both) to fill up the small spaces between the granules. A protective waterproof varnish is applied, and on this is spread an orthochromatic emulsion, so that the plate is complete in itself—photographic plate and colour screen in one. It is exposed on the camera exactly as usual, except that the glass side of the plate is put towards the lens, so that the light has to pass through the layer of coloured starch granules before it affects the sensitive film. The plate is developed, and the resulting negative, instead of being fixed, has the metallic silver that constitutes the image dissolved away, and the remaining silver salt reduced to the metallic state, thus transforming the negative into a positive. When viewed as a transparency, the colours as well as the form of the original are seen. The preparation of these plates must be regarded as a triumph of manufacturing skill. Some very excellent results have been obtained with them, but the colours are readily affected by error in their treatment. The "grain" of these plates is not so fine as one might suppose from the fact that starch granules are used, for it is apparently impossible to thoroughly mix the differently coloured granules. They occur on the plates in groups up to a dozen or more of one colour, and the groups are visible by a magnification much too low to show the individual granules.

A one-plate process such as that just described obviously must have the same dyes for taking the photograph, that is for dividing the colour of the original into the three fundamental colours, as for viewing the result, and this is a disadvantage. It is due to the wide permissible choice of colours and the non-critical comparison of the resulting colours with those of the original that the results are acceptable. These plates reproduce the colours of the spectrum very poorly. Presumably in the selection of dyes the best compromise has been made for such photography as the plates will generally be used for. It is practically impossible to multiply such colour photographs by exposing a new plate to light under a finished plate, because, as we have seen in the first plate, two-thirds of the light is lost, and the effect of making such a copy would be to lose two-thirds of the light passing through the first. Such a copy would, therefore, have about eight-ninths of its surface dark, reducing the light that would otherwise be available to about one-ninth, and it would be so dark as to be almost useless. Mr. Powrie has shown how it is possible to overcome the difficulty when using his plates, by fixing a mirror on each side of the printing-frame so that the light impinges on the plate from three directions, and then by suitably separating the two plates by a sheet of glass or celluloid every line in the upper plate—the picture—can be made to give a line of three times its width on the lower plate. So each of the three colours in the upper plate covers the whole surface of the lower plate, and no light is lost. By using light that corresponds to one colour only, it is possible by this means to get a record of that colour on an ordinary plate that is continuous—that is, that covers its whole surface instead of being as the original is, in lines that cover only one-third of its surface. Three separate continuous colour records, one for each colour, can thus be obtained from the original single plate, and any three-colour process can be worked from these records.

The subtractive method, in which the three coloured prints are superposed, and each subtracts its quota from the light that passes through, was foreshadowed by Du Hauron and by Charles Cros. The production of transparencies in this way engaged the attention of Mr. Ives, and in 1893 he showed me a very fine example, perhaps 8 in. by 6 in. or larger. But it is to Mr. Sanger-Shepherd and his firm that we owe the establishment of this process, and the supply of the necessities for it, so that it can be worked by any one who wishes to do so. The usual three colour records are obtained; the one from the red screen is printed on a lantern transparency plate and the image is toned to a greenish blue colour, and the other two records are printed on bichromated gelatine films supported on celluloid, exposing through the celluloid. These, after development in warm water, are stained by suitable dyes, and then mounted on the greenish blue image, preferably by cementing them together with Canada balsam. One advantage of this method is that the three coloured images can be tentatively placed together, and if one colour is predominant a little of the dye can be washed out from that print, while if one is deficient it can be stained deeper. A somewhat similar method was introduced in 1895 under the name of "Pinatype" by Messrs. Meister, Lucius & Brüning. Three transparencies are prepared from the ordinary three negatives, and under each of these is exposed a sheet of bichromated gelatine. These gelatine prints are washed, and each is immersed in its appropriate dye solution. The dye is absorbed where the gelatine has not been acted on by light, but where the combined action of light and the bichromate has fully affected it, it is hardened and does not absorb the dye. These are called "print plates," for their function is to give up the dyes they have absorbed to a sheet or glass coated with a soft film of gelatine, which is pressed into optical contact with each "print plate" in turn. The "print plates" can be used repeatedly. Messrs. Sanger-Shepherd have perfected a somewhat similar method for making colour prints on paper, but their gelatine prints, which absorb the dye and then give it up to form the final picture, are developed in warm water and so form low reliefs. As "carbon" prints can be made in any colour, some of the firms that make carbon tissues have devised methods by which three carbon prints are made of the required colours from the three colour record negatives and then superposed.

As any method by which the three coloured impressions can be superimposed on paper will give a three colour print, various printing-press methods are available, and some exceedingly fine work has been done by collotype printing, the printing surface being of hardened gelatine and inked up with printers' inks. But the process that is of all the most advantageous, especially where many impressions are wanted, consists in the preparation of three "half-tone" blocks, one corresponding to each of the three colour records, and making from these three superposed impressions in the three necessary colours. The greatest difficulty of these methods is in the getting of suitable inks, for they should not only be of the correct colour, but they (or at least two of them) should be transparent, and they should be permanent. The most suitable colouring matters are too fugitive, so theory has to be compromised, and as none are really transparent there is always a tendency for the colour last printed to predominate. In spite of these drawbacks very excellent work is done commercially by this process, but probably never without "fine etching"—that is, proof impressions from the blocks are compared critically with the original by persons who have been trained to appreciate colour and drawing; and where the tints are incorrect the alterations required are marked on the impressions, and the blocks are returned to the etcher, who works on the faulty part. In the best work this proofing and correction is repeated until the result is satisfactory. The "half-tone" block prints a series of dots equidistant from their centres and larger as the tone or shadow is deeper. In superposing the three impressions no attempt is made—indeed it would be practically impossible—to print the corresponding dots exactly over each other, and the result is that sometimes the dots are superposed and sometimes juxtaposed, according to chance. This might appear to lead to a mixture of the additive and subtractive effects, and as the colours for the one method must be the complementaries of those used in the other, it might be supposed that confusion would result. It is not so, however. Where only one ink is required, and where all three are required to their fullest extent to give black, the case is simple. Take the intermediate case of a grey produced by juxtaposition only of the three inks and in such a manner that the white paper is completely covered. As each ink absorbs one of the three fundamental colours, we may describe the grey roughly as one-third black and two-thirds white. If now the three colours are superposed they will produce black, but only one-third of the area of the spot of white paper concerned will be covered, so that the result will be actually one-third black and two-thirds white—practically as before.

In all the processes so far considered the colour has been produced by light, or its distribution has been controlled by it. But there is a radically different method that has been in the minds of those interested in these matters for nearly thirty years, and latterly has been worked upon by many investigators with more or less, but on the whole gradually growing, success. The three necessary colours are put on the paper to begin with, and the light destroys or bleaches those that are not wanted. The method depends upon the fact that light can affect a substance only when it is absorbed, and therefore when a mixture of unstable coloured substances is exposed to coloured light, there is always a tendency for those substances that are of the same colour as the light to survive the longest, because they reflect more of the light than the others. The difficulties in working out such a method are many. The three dyes must be of the right colours, they must be about equally bleachable by white light, they must be readily bleached or the exposure would be too prolonged, and it is desirable that they shall be rendered more stable after the exposure. Dr. J. H. Smith of Zurich about a year ago put this method on a commercial footing and issued the paper ready for exposure beneath the coloured original under the name of "Uto" paper. The colours are made more sensitive by the addition of anethole, and after the exposure the print is soaked in benzene or acetone to remove the sensitiser. This paper gives surprisingly vivid reproductions of the colour of the original, but obviously the prints are not very stable to light.

Thus the present practical methods of colour photography are "three-colour" methods, and they do not aim at reproducing colour, but only at imitating it. If the imitation is perfect by daylight it will probably be faulty by artificial light, and a spectroscopic analysis of the two colours will at once show their differences. The perfection of the imitation depends upon the skill of the worker as well as upon the characteristics of the method. The colour of the photograph is not impersonal evidence of the colour of the original; but the same qualification applies to the vast majority of observation records. This much, however, may be said in favour of three-colour processes—if a series of photographs is made by the same process and with the same materials, the discrepancies of colour would probably be more easy to trace than the random errors possible when the colouring is done entirely by hand. Moreover, any one who is accustomed to photographic manipulations and others with practice can work some of the processes, while it must be the comparatively few who can ever hope to become skilled in applying colours with the brush.

THE EFFECTS OF ENVIRONMENT AND NUTRITION UPON FERTILITY

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Experienced breeders of animals have seldom failed to recognise that the generative system is particularly susceptible to changed conditions of existence. Buffon long ago commented on the fact that the domestic animals are as a rule far more prolific than their wild representatives, and Darwin, who made the same observation, was disposed to ascribe the increased fertility of the former to a long habituation to a copious food supply without the labour of seeking for it. On the other hand, it is equally well known that wild animals when brought into captivity often become sterile, while there are numerous instances also of domestic animals failing to breed as a result of removal to a new environment. Such sterility, when it occurs, is not necessarily (or even generally) associated with disease or want of vigour, for, as Darwin observed, wild animals in confinement are not infrequently notoriously healthy and long-lived, and nevertheless fail consistently to produce young. There is no evidence that the reproductive organs are themselves diseased, yet they seem incapable of performing their natural functions. Moreover, in those cases in which wild animals in captivity have proved fertile, the capacity to breed is not necessarily inherited by their offspring, although, as a general rule, the fertility tends to increase in subsequent generations. Thus, it was a considerable time before the canary bird was fully fertile, but it eventually became so, whereas certain of the nearly related finches, while producing hybrids with the canary, only occasionally reproduce their own kind when kept in captivity. Other wild birds again, such as most members of the great families of ducks, pigeons, and fowls breed as readily in confinement as in their natural state. Similar differences occur in the various groups of mammals. For instance, bears breed less freely in the Zoological Gardens than most other carnivores, although it is difficult to assign a reason for this fact. Furthermore, it was pointed out by Darwin that close confinement cannot be regarded as a sufficient explanation of infertility in such cases, since the semi-domesticated ferret, for example, breeds readily when kept in closely cramped hutches.

There can be no doubt that those environmented conditions which are conducive to the occurrence of "heat" or œstrus are generally also favourable to fertility, for although it is true that many animals which have never succeeded in producing offspring in captivity have been observed to experience œstrus and indulge in sexual intercourse, there can be no question that a prolonged or frequently recurring sexual season is usually associated with an increased capacity to bear young. The origin of the breeding season has been discussed in two papers by Mr. Walter Heape,[1] who lays considerable stress on the part played by nutritive influences, as shown especially by the effects of certain stimulating foods upon the generative functions of sheep. But it is none the less evident that nutrition is not the sole factor in determining the time for breeding, for, as Mr. Heape points out, its occurrence is to a great extent seasonal, and is governed both by external forces (*e.g.* climatic influences) consequent upon periodic change, and by internal forces dependent on the inherited capacity of the individual.

Some interesting observations made by Mr. Bles on various kinds of Amphibia seem to have a bearing upon this question.[2] This observer shows that axolotls, as well as certain species of frogs and newts, can only be induced to breed in captivity in the presence of particular environmented conditions. Mr. Bles found that by feeding them copiously in summer and allowing them to hibernate in winter, and afterwards suddenly transferring them to an aquarium stocked with growing plants and provided with running water or with suitable pond water, these animals could be induced to spawn within a few days. He draws the conclusion that the difficulty so often met with in inducing Amphibia to breed is not due to any toxic influence on the gonads resulting from close confinement, but should rather be ascribed to the absence of the necessary external stimuli without which the generative organs of animals are incapable of discharging their functions. This view may also help to explain why some animals (*e.g.* insects) make their appearance in great numbers in one year and are comparatively scarce in another.

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[1] Heape, *Quart. Journ. Micr. Science*, vol. xliv. 1900; *Proc. Royal Soc.* B, vol. lxxvi. 1905.

[2] Bles, *Trans. Royal Soc. Edinburgh*, vol. xli. 1906.

In those animals which, as a general rule, breed readily in a state of domestication or confinement, it is probable that nutrition plays the most important part in regulating the capacity to produce offspring. That an insufficient or markedly abnormal diet must affect this power is almost self-obvious. It is also clear that the effects of excessive nutriment are likewise prejudicial to the proper discharge of the reproductive functions. No better example could be given of the way in which over-feeding results in a condition of sterility than that afforded by the barren Shire mares which have been a noticeable feature at recent agricultural shows. Breeders of cows and sheep have learnt from long experience and at great cost the disastrous consequences of an over-nourishing diet upon the fertility of their stock. It would seem, however, that owing to the desire to excel in the showyard breeders of draught horses are falling continually into the old error. In the classes provided for barren Shire mares there are invariably to be found some of the finest specimens of the breed, so that those animals which appear best calculated to produce a superior class of foals are useless for stock-breeding purposes. Little or nothing is certainly known regarding the way in which excessive feeding checks the tendency to conceive, but this result may probably be ascribed to fatty degeneration in the organs of reproduction.

It is a somewhat remarkable fact that, although numerous experiments have been undertaken to determine the effects of different methods of treatment upon wool, meat, or milk production, no systematic attempt had been made until quite recently to deal with the factors which influence fertility in livestock. A few years ago, however, the Royal Agricultural Society instituted an inquiry into the causes of barrenness and abortion among different breeds of sheep in the south of England. The investigation was conducted by Mr. Heape, whose report was subsequently published in the *Journal* of the Society.[1]

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[1] Heape, "Abortion, Barrenness, and Fertility in Sheep," *Jour. Royal Agric. Soc.* vol. x. 1899.

In this report it is shown that in the season 1899 the proportion of ewes which failed to breed or which aborted their lambs was 6·76 per cent., and that the number which produced twins was about 30 per cent. The most fertile of all the breeds was the Wensleydale, in which six flocks consisting of a total of 319 ewes produced a percentage of 177·43 lambs. The effects of locality are also discussed, and there is an accumulation of evidence which seems to indicate that the character of the district is not without influence on the fertility of the breed. Thus the records show that whereas the sheep belonging to the Lincoln variety in Yorkshire produced an average of 47·57 per cent. of twins, those in the home county had only 25·11 per cent., while those in neighbouring counties produced 33·78 per cent. With other breeds the variation in the fertility in different districts, while quite noticeable, was not so pronounced as in the Lincoln sheep.

The report shows, further, that the fertility of a flock depends greatly upon its management, that the quality and quantity of the food supplied affect the condition of the sheep and so influence their capacity to breed, that some seasons are far more favourable to fertility than others, and that sheep-stained pasture (*i.e.* pasture on which sheep have recently been kept for some little time previously) is often prejudicial to breeding stock.

As a result of a recent investigation upon the reproductive processes in sheep, it has been shown that (in the breeds investigated) the normal percentage of Graafian follicles discharging their ova at any single "heat" period does not appreciably exceed the usual percentage of births at the lambing season. It would seem, therefore, that a comparative scarcity of twins at lambing time is almost certainly directly correlated with an abnormally small number of ripe follicles in the ovary at tupping time (*i.e.* during the breeding season). An unusually low percentage of twins is closely associated with barrenness. This fact is generally recognised by flockmasters, and Mr. Heape's statistics prove it very clearly. And since habitually (*i.e.* constitutionally) barren ewes are a rarity, there can be little doubt that barrenness is due normally to the same cause operating on a more exaggerated scale—*i.e.* to the absence or great scarcity of Graafian follicles available for ovulation during the tupping season.[1]

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[1] Marshall, *Phil. Trans.* B. vol. cxcvi. 1903.

Scarcity of ripe follicles at tupping time must clearly result either from retardation in follicular development or from an unusual amount of follicular degeneration, either recently or at some previous period in the animal's lifetime. Degeneration of follicles is by no means uncommon in the ovaries of sheep, and appears to be most frequent in those which have attained to from one-eighth to one-half the dimensions of the mature follicle. It may set in, however, at practically any stage of development. The follicle, instead of continuing to grow, undergoes a series of retrogressive changes, which result in the shrivelling up of the ovum and the ultimate absorption of the entire contents of the follicle. There can scarcely be any doubt that the degeneration is usually the result of an insufficiency of stimulating power at the disposal of the ewe.

That scarcity of mature follicles in sheep's ovaries at tupping time may be due to retardation of growth is a conclusion that is based on inference rather than on direct observation, for little is known concerning the rate of development of the Graafian follicle. There is every reason for believing, however, that the process of ripening can be very largely influenced both by insufficiency of food supply on the one hand, and by artificial stimulation on the other.

This fact has been perfectly well realised for years past by certain individual flockmasters, who have consistently practised the methods of flushing or artificially stimulating their sheep by means of an extra supply of special food at the approach of the breeding season. It is somewhat surprising, however, that no precise records of the effects of flushing upon fertility had been collected until quite recently, when the Highland and Agricultural Society of Scotland undertook an inquiry upon this subject. The absence of published information may perhaps explain the prevalent ignorance of the results of flushing among many sheep-breeders who have never adopted it.

In a preliminary report upon the Highland Society's investigation[1] containing the lambing statistics for various Scottish breeds in the year 1905, it is shown that the percentage of lambs born was, as a rule, largest among flocks which had been subjected to a process of artificial stimulation. The method adopted was to feed the ewes upon turnips, oats, dried grains, maize, or other artificial food at the tupping time and for about three weeks previously, while maintaining them upon grass only during the greater part of the year. Some flocks, however, received a limited quantity of additional food (turnips, etc.) during pregnancy, and especially during the latter part. The statistics show that in the flocks which were treated in this way the percentage of lambs per ewes[1] was considerably in excess of the average percentage for flocks which received no special treatment, while the percentage of barren ewes was generally appreciably less. In some cases the number of lambs per ewes[1] in the flushed flocks was nearly 200 per cent. Among flocks of the same breeds (Border Leicester or half-bred Border Leicester) which received no sort of special treatment, the average proportion of lambs per ewes[1] was between 150 and 160 per cent., while flocks which were placed upon superior pasture at the approach of the breeding season (without being otherwise specially fed) generally produced a slightly larger percentage of lambs (about 160 per cent.).

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[1] Marshall, *Proc. Royal Soc.* B, vol. lxxvii. 1905.

It may be of some interest to describe more precisely the method of treatment adopted for certain of the flushed flocks in which a relatively large number of twin lambs were produced.

In one of these the ewes (which were half-bred Border Leicester by Cheviot) were fed upon grass only during the summer previous to tupping. For three weeks (during tupping, beginning of October) they were allowed a full supply of turnips upon grass. Between tupping and lambing (five months) they were given a mixture of dried grains and turnips, and lamb food for three weeks before lambing. The rams (which belonged to the pure Border Leicester breed) were fed upon bruised oats during tupping. The percentage of lambs per ewes[1] was 191·5. One ewe had four lambs and 12·5 per cent. had triplets. None of the ewes were barren and none aborted.

In a second experiment the ewes (which were also half-bred), after being kept upon grass during the summer, were supplied with Bombay cake, bruised barley, and a little linseed, as well as turnips and cabbages during the tupping season. Some turnips were given during pregnancy. The rams (Border Leicester and Oxford Down) were treated in the same way. The percentage of lambs per ewes[1] was 193·75. None of the ewes aborted and none were barren. Triplets were produced in 13·5 per cent. of the ewes.

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[1] That is to say, the number of lambs per 100 ewes.

In a third case the ewes (half-bred) were placed upon superior pasture at tupping, and from that time onwards until lambing they were supplied with hay and turnips. Previous to tupping they were fed upon grass alone. The rams (Border Leicester, Oxford Down, and Cheviot) were treated similarly to the ewes before and during tupping. The percentage of lambs per ewes[1] was as high as 196. Out of 184 ewes 23 had triplets. Two ewes aborted and one was barren.

In another experiment 60 ewes were placed upon rape and seeds at tupping time. Of these, 54 produced either twins or triplets at the following lambing, the proportion far exceeding that in the other sheep which were upon the same farm but not similarly treated.

The Highland Society's investigation is still in progress, and a full report will not be issued until next year. In the meantime it may be stated that further experiments fully confirm the conclusion that stimulation of the generative organs of sheep by a system of special feeding at the beginning of the breeding season results in an increased crop of lambs at the following lambing season. The twins appear almost invariably to have been born early during lambing, thus showing that the reproductive activity of the ewes is usually greatest at the beginning of the breeding season.

There is abundant evidence also that flushing tends to hasten the time for breeding. It has been shown recently that the condition of "heat" in animals is probably brought about through the action of an internal secretion or chemical excitant elaborated by the ovaries.[2] It would seem, therefore, that the artificial feeding exercises a stimulating influence over the secretory activity of the ovaries, while at the same time promoting the more rapid growth and maturation of the follicles, and causing a larger number to discharge their ova at the earlier "heat" periods of the breeding season.

It has so far proved more difficult to obtain precise information regarding the effects of flushing in one season upon the fertility of the sheep in after-years. The more usual experience of those flockmasters who have practised flushing appears to be that this process is not in any way detrimental unless it is over-done. If the artificial feeding is excessive, and the sheep are made to depend for the rest of the year (*i.e.* during gestation and afterwards) upon nothing better than sustenance diet, one might reasonably expect the ewes to deteriorate, and their subsequent fertility to be impaired. It is apparently for such a reason as this that some breeders, especially in England, regard the practice of flushing as altogether to be deprecated. In this connection it should be mentioned that there is some evidence for the belief that if sheep are flushed in one year, the process must be repeated in the next, and that if this practice is not adopted, the ewes tend to be less fertile than if they had never been flushed at all.

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[1] That is to say, the number of lambs per 100 ewes.

[2] Marshall and Jolly, *Phil. Trans.* B, vol. cxcviii. 1905. Cf. also Knauer, *Arch. f. Gynäk.* vol. lx. 1899; and Halban, *S.B. Akad. Wiss.* Wien, vol. cx. 1901.

On the other hand, certain of the reports show that sheep which produce twins one year, in a large proportion of cases bear twins also in the year following. This appears to occur irrespectively of flushing. It would seem, therefore, that an increased degree of fertility is a characteristic of certain particular ewes.

Before concluding this brief summary of recent investigation upon certain of the factors which control fertility, I may take this opportunity of urging the importance of further inquiry in the interests of the livestock industry. In these days, when much is heard of agricultural depression, it is not always realised that the breeding of domestic animals is one of the staple industries of the country. The prominent position which British horses, British sheep, and British cattle still hold in the livestock markets of the world is, perhaps, the most hopeful indication for the future of British agriculture. It is a sufficiently remarkable fact that, excepting for the Holstein cattle, the Percheron horses, and the Merino sheep, all the prominent breeds of livestock throughout the world have their foundation in animals of British ancestry.

Even the Percheron horses are not the equals of the English Shires for stamina and power. Nearly every good horse on the Continent and in America is derived from British stock. The famous American trotters are descended from English hackneys. At the international conference of sheep-breeders which recently met at Ipswich, great stress was laid upon the high favour in which British sheep are always held by the great cosmopolitan buyers. The livestock export from Great Britain goes on increasing year by year, and last year was phenomenal, reaching a grand total value of a million and three-quarter pounds.

And yet, despite its comparative prosperity, it is very evident that the breeding industry suffers annually from no inappreciable loss. The prevalent sterility among the better class of Shire mares has already been alluded to, while incapacity to breed is perhaps still commoner among Thoroughbreds, for the Royal Commission on Horse-Breeding showed that no less than 40 per cent. of the country's thoroughbred mares fail to have foals each year. Among cattle the annual loss from sterility has been estimated at 15 per cent., while it is shown in the report of the Royal Agricultural Society on fertility in English sheep for the year 1899 that the proportion of ewes which failed to breed was over 6½ per cent. In view of the facts of which these are only examples, it is sufficiently obvious, as Mr. Heape has pointed out, that any means by which sterility can be reduced and the capacity to bear young increased must be possessed of great commercial value. And this result can only be attaiend by continuous scientific investigation and the introduction of scientific method into all the problems of practical breeding.

Mr. Heape, in his work on *The Breeding Industry: Its Value to the Country and its Needs*, has shown from statistical evidence that the amount of money invested in livestock in this country must be computed at scarcely less than £450,000,000. Adding to this the capital spent on buildings, land, vehicles, and various accessories, the total becomes still more gigantic. And yet what Mr. Bateson said at the Cambridge meeting of the British Association three years ago is still almost true: "Breeding is the greatest industry to which science has never yet been applied." It cannot be doubted that the introduction of rigorous scientific method into the breeder's industry will be attended by immense advantage, just as it has proved invaluable to other industries.

WORK UNDER PRESSURE AND IN GREAT HEAT[1]

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THE development in all directions of engineering and manufacturing work is constantly bringing man into new and unaccustomed relations with his environment. In consequence of this, his working efficiency may be reduced very greatly, and his health, or life itself, may be endangered. The question of how to carry on work safely and efficiently under an unwonted environment is thus one which occurs in many forms to those who are engaged in our branch of science. In the present address I wish to glance shortly at several problems of industrial hygiene, presented by work beneath water or beneath the ground, and at some recent attempts at their investigation and practical solution.

I shall refer first to work in deep water under the sea. In consequence of the difficulties and dangers connected with the work of divers on the sea-bottom, the British Admiralty two years ago appointed a Committee to investigate the subject, with myself as the physiological member. The experiments carried out by this Committee, and at the Lister Institute, London, in close connection with it, are now completed; and I propose to give some account of the results, which, like many other British investigations on questions of hygiene, are hidden under the somewhat forbidding form of an official blue-book.[2]

Let me remind you that the ordinary diving dress consists of a copper helmet screwed to a corselet, the latter being in its turn connected water-tight to a stout waterproof dress covering every part of the body except the hands, which project through elastic cuffs. Air is supplied through a non-return valve on the helmet from a flexible pipe connected with an air-pump on a boat or ship: the air escapes through an adjustable spring valve at the side of the helmet. The arrangement is thus such that the pressure of the helmet air breathed by the diver is always equal to, or slightly greater than, the pressure of the water at the valve outlet. At a depth of 10 metres (33 ft.) the diver is therefore breathing air at an excess pressure of 1 atmosphere, or at an absolute pressure of 2 atmospheres; and every additional 10 metres will add another atmosphere to the pressure.

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[1] An address delivered at the General Meeting of the International Congress of Hygiene, Berlin, September 26th, 1907.

[2] *Report to the Admiralty on the Conditions of Deep Diving*, 1907.

Provided that about 50 to 100 litres of air per minute are supplied to the diver, and that the outlet valve of his helmet is properly adjusted, he can work quite comfortably at depths up to about 20 metres. Beyond this depth, however, he usually feels increasing discomfort and difficulty in working; so that at 40 or 50 metres work becomes extremely difficult. This difficulty has hitherto been ascribed to the pressure: its real cause was one of the first points which we investigated. We found that the discomfort of the diver was associated with laboured or dyspnœic breathing; and this fact, in connection with the results of recent experiments on the normal regulation of breathing, suggested the true explanation.

In a paper published two years ago by Mr. Priestley and myself,[1] it was shown that under normal conditions the breathing is always regulated in such a way as to keep the partial pressure of the carbon dioxide in the air of the lung alveoli almost exactly constant. This fact was established by analysing samples of air from the lung alveoli in man. To obtain a sample all that is necessary is to make a sudden deep expiration (during perfectly natural breathing) through a long piece of tubing of wide bore, and at once withdraw into a gas-analysis apparatus a portion of the air left in this tube at the end of expiration. The deep expiration washes out all the more or less pure air contained in the air-passages and tube before the deep expiration, and leaves the tube full of pure alveolar air. This pure alveolar air contains for each individual an almost astoundingly constant percentage of CO_2 if the barometric pressure is constant. If the barometric pressure varies, the percentage of CO_2 varies inversely as the barometric pressure, so that the partial pressure of CO_2 remains constant. For instance, we found in ourselves that the mean percentage of CO_2 in our alveolar air was 6·01 at normal pressure, and 3·53 in compressed air at 1·7 atmospheres absolute pressure. The corresponding partial pressure of CO_2 in the alveolar air was 5·68 per cent. of an atmosphere, or 43 mm. of mercury, during respiration at normal pressure, and exactly the same in the compressed air. Thus the respiratory centre normally responds only to variations in the partial pressure of CO_2 in the blood which irrigates it. To variations in the partial pressure of oxygen it is within very wide limits absolutely indifferent. Only when the partial pressure of oxygen in the air inspired falls below about two-thirds of the normal does the respiratory centre begin to respond to want of oxygen. Quite recent experiments by Hill and Greenwood at high pressures in air, and by Boycott and myself at low pressures in a mixture of oxygen and air, have shown that at an absolute pressure of 6 atmospheres the alveolar CO_2 percentage was 0·9, and at 0·4 atmospheres it was 15; while at normal pressure it was about 5·5 with the same individuals. The partial pressure of CO_2 (*i.e.* the percentage in the moist alveolar air multiplied by the barometric pressure) remained, however, quite constant.

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[1] *Journal of Physiology*, vol. xxxii. p. 225, 1905.

If CO_2 is present in the air inspired, the effect is to make the breathing deeper, and finally also more frequent; unless, however, the pressure of CO_2 in the inspired air begins to approach the normal alveolar CO_2 pressure, there is very little change in the alveolar CO_2 pressure, compensation being produced very easily.

How, now, does this apply to the case of the diver? On account of the work involved in pumping, a diver has to content himself with a minimum supply of air. Let us suppose that when he is just under water he has sufficient air to prevent the CO_2 percentage in the helmet air from rising beyond 3 while he is at work. This will keep him fairly comfortable. If he now goes down 10 metres, the air supply being the same, the percentage of CO_2 in the helmet air will also remain the same. As, however, the pressure is now 2 atmospheres, his normal alveolar CO_2 percentage will be 2·8 instead of 5·6. It will, however, be quite impossible for him to maintain this percentage of CO_2 in his alveoli, since during work the percentage in the inspired air itself is 3. He will thus suffer from severe dyspnœa. A very little consideration will show that the diver must have twice as much air at 10 metres if he is to be as comfortable as he was at surface; and at whatever depth he may be his minimum air supply must be increased in proportion to the increase in the absolute air pressure. In other words, the minimum *volume* of air supplied to him, measured at the pressure he is under, must always remain the same.

To cut a long story short, we found that as soon as this condition was realised, as proved by numerous analyses of air from the helmet, the discomfort and loss of working power in deep water disappeared. Lieutenant Damant and Gunner Catto, the two officers who carried out most of the experiments in deep water, and who reached the greatest depth hitherto definitely recorded, were as free from respiratory distress at 64 metres (210 ft.) as at 1 metre. They could also reach this depth easily within two minutes, which showed the extraordinary fallacy in the time-honoured tradition that a diver should always descend slowly, so as to accustom himself by degrees to the change of pressure.

By guarding against excessive increase of CO_2 pressure in the air breathed by a diver, we not only increase greatly his working efficiency and comfort, but also obviate a serious danger. It not infrequently happens that a diver, particularly if he is somewhat unskilled, becomes unconscious or stupefied by the effects of CO_2. The consequences of this may easily be fatal, as it is very dangerous to draw a man up rapidly from a great depth if he has been down for any time; and also dangerous to leave an unconscious man on the bottom.

In connection with the effects of CO_2 in a diver's helmet, I should like to say something as to the presence of CO_2 and other impurities in the air of mines. It is well known that an excess of CO_2 and corresponding deficiency of oxygen is commonly met with in the air of mines, and that certain kinds of mining work are very unhealthy—particularly the mining of some of the more valuable metals, such as gold, tin, silver, copper, and lead. On account of the high death-rate and large amount of illness among the tin-miners of Cornwall in England, I was asked in 1902 by the British Government to investigate the ventilation of the mines there. It was known from the results of an earlier inquiry,[1] confirmed by my own analyses, that it is easy enough to find many working places in these mines where the proportion of CO_2 rises to as much as 50 volumes per

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[1] *Report of the Royal Commission on Metalliferous Mines*, 1864.

10,000 of air, or higher; and much stress had been laid on the gaseous impurities of the air as explaining the ill-health of the miners. The physiological data already mentioned prove, however, that although an actual rise of ½ or 1 per cent. in the alveolar CO_2 pressure would have most violent physiological effects, no such rise actually occurs when air containing ½ or 1 per cent. of CO_2 is breathed. The only effect is that the breathing becomes very slightly deeper, the difference being subjectively quite inappreciable. Less than 1 per cent. of CO_2, or 100 volumes per 10,000, is therefore of no importance in air at ordinary pressure, provided no other harmful inpurity is present. Except in exceptional cases—for instance, just after blasting—there was no evidence of any other harmful gaseous impurity in the mine air; and by far the greater part of the CO_2 was found to arise from the slow oxidation of mineral matter such as iron pyrites (FeS_2), with consequent liberation of CO_2 from carbonates by the sulphuric acid formed.

What, then, was the cause of the ill-health of the Cornish miners? Further examination[1] into the facts disclosed two causes. The first was that certain of the mines were badly infected with ankylostomiasis, which, as has so often been the case during the last hundred years, had not been recognised, and which was soon brought under control by suitable measures. The second, and by far the more serious, cause was the fact that dust raised locally by drilling and blasting granite, quartz, and other hard stone was being inhaled by the miners and causing injury to their lungs which produced a marked predisposition to tubercular phthisis. The increased death-rate among the miners was due entirely to lung disease, chiefly tubercular phthisis. During middle life, for instance (age thirty-five to forty-five), the death-rate from lung disease was 33 per 1,000 among Cornish miners, as compared with 3·4 per 1,000 among coal and iron miners; and from all other causes 5·8 per 1,000 among Cornish miners, and 6·5 per 1,000 among coal and iron miners. An investigation of the working history of each man who had died in one of the mining districts during a period of three years revealed the fact that the extra deaths—at any rate during middle life—were confined almost entirely to men who had been engaged either locally or abroad in the dustiest work—namely, the management of machine drills worked by compressed air. By the use of water jets or other means, which I need not specify in detail, the inhalation of stone-dust from these drills and from blasting can be entirely prevented; and legislation rendering effective means compulsory was carried through at once with the full support of the management of the mines.

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[1] *Report on an Outbreak of Ankylostomiasis in Cornish Mines;* and *Report on the Health of Cornish Miners*, Parliamentary Papers, 1902 and 1904.

The accompanying tables show some of the Cornish statistics:

TABLE I

Annual Deaths per 1,000 *living at each age*

	Ages					
	15–20	20–25	25–35	35–45	45–55	55–65
All miners (Cornwall):						
Lung diseases	0·7	2·7	17·3	33·2	32·2	42·6
All other causes... ...	1·0	3·1	3·6	5·8	12·4	27·9
Coal miners (England):						
Lung diseases	0·9	2·0	2·1	3·5	7·8	18·7
All other causes	2·9	3·6	4·2	6·5	11·6	25.1
Ironstone miners (England):						
Lung diseases	1·6	1·5	2·1	3·2	6·5	13·0
All other causes	1·8	3·1	3·8	5·0	10·6	20·3
All occupied males (England):						
Lung diseases	0·95	2·7	3·7	5·9	8·6	13·0
All other causes	1·6	2·4	3·6	6·5	12·9	20·7

TABLE II

Deaths of all men who had ever worked Machine Drills, and who died in Redruth District, Cornwall, 1900-2

	Ages					Total.	Mean Age at Death.	Mean Duration of Machine Drill Work.
	15–25	25–35	35–45	45–55	55–65			
Lung diseases	3	51	54	22	3	133[1]	37·2	7·0 years
All other causes	2	4	1	2	0	9	—	—

It is a remarkable fact that while the inhalation of dust from hard stone is extremely dangerous when habitually inhaled, the dust from coal, or soft stone, and many other materials, has no such effect, at least in moderate quantities. An average English coal-miner inhales very large amounts of coal-dust; but coal-mining is one of the healthiest of all occupations, in spite of absence of light, exposure to extremes of temperature, and the inhalation of air which is, chemically speaking, far from pure. It just happens that the ordinary impurities—moderate excess of CO_2, CH_4, dust from coal and shale, and deficiency of oxygen—matter comparatively little from the health point of view, whereas dust from hard stone matters a great deal.

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[1] Of these, 122 were returned as phthisis.

I must now return to deep diving. The most formidable danger presented by this occupation occurs only on the ascent of a diver to surface. It has been known for long that divers and other workers in compressed air are subject on their return to surface to a variety of serious symptoms—in mild cases only pains in the limbs or elsewhere (usually known among English workers in compressed air as "bends"); in more serious cases paralysis, either temporary or permanent, particularly of the legs and bladder; or, finally, symptoms of asphyxia, which may prove rapidly fatal. The classical experiments of Paul Bert[1] proved, thirty years ago, that all these symptoms are due to liberation of gas-bubbles in the blood or elsewhere within the body; and considerable further light has been thrown on this subject by more recent work, including particularly that of Catsaras, von Schrötter,[2] and Hill. It was on the prevention, rather than on the pathology, of these symptoms, known collectively as caisson disease, that the Admiralty Committee concentrated its attention. The blood and body tissues become saturated with gaseous nitrogen in accordance with Dalton's Law during exposure to compressed air. On rapid decompression this gas liberates itself in the blood as bubbles, which cause local or general blocking of the circulation, with corresponding symptoms. Paul Bert showed on animals that in order to avoid this condition decompression must be slow; but the question, How slow? had not been satisfactorily answered in the case, at least, of man. The nearest attempt at an answer was that of von Schrötter and his colleagues, based in part on theoretical considerations suggested by Zuntz, and evidently to a large extent correct. In many points, however, it seemed to us that von Schrötter's conclusions were open to criticism. Practical experience, for instance, seemed to show that it takes far longer than he believed for the human body to become saturated with nitrogen in compressed air, and a correspondingly longer time to become desaturated. Similar criticisms applied to the conclusions of Hill and his colleagues on this subject.[1]

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[1] *La Pression Barométrique*, 1878.

[2] Heller, Mager, and von Schrötter, *Die Luftdruckerkrankungen*, Vienna, 1900; von Schrötter, *Der Saurerstoff in der Prophylaxie und Therapie der Luftdruckerkrankungen*, 2nd ed., Berlin, 1906.

It was evidently necessary to make further experiments, and these were rendered possible in England by the gift to the Lister Institute by Dr. Ludwig Mond, F.R.S., of a large experimental steel chamber capable of comfortably taking a number of animals or several men. In this the experiments were carried out by Dr. A. E. Boycott, of the Lister Institute, Fellow of Brasenose College, Oxford, and Lieutenant Damant, the naval officer who, as already mentioned, was also engaged in experiments on himself and others in deep water at sea. For the experiments on animals goats were selected, as we were convinced from the outset that small animals, in consequence of their rapid circulation, were useless for our purpose. Indeed, very small animals showed no symptoms whatsoever after exposures from which rapid decompression killed goats with certainty, and *a fortiori* would have killed men. With long exposures to high pressures the risks to be guarded against on decompression are undoubtedly still greater in men than in goats.

Several hundred decompressions of goats, men, and other animals have been carried out during 1906 and 1907 by Boycott and Damant. In the time available I cannot, however, give more than an outline of some of the results.

In the first place it was found that, with equal conditions as regards decompression, the symptoms observed in goats increased in danger and severity as the duration of exposure increased up to at least two hours or perhaps somewhat more. This is illustrated in Table III., showing some of the results:

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[1] *Journal of Hygiene*, vol. iii. p. 436, 1903; *Proceedings of the Royal Society*, vol. lxx. p. 455, 1903; vol. lxxvii. p. 442, 1906; vol. lxxix. p. 21, 1907.

TABLE III

Absolute Pressure 4 Atmospheres

Exposure in Minutes.	Decompression in Minutes.	Number of Goats.	Cases of "Bends."	Severe Symptoms.
15	1	15	1	0
30	1	15	3	0
60	1	14	4	0
120	1	10	2	4
60	10 (uniform)	11	3	1
120	10 "	11	4	1
240	10 "	11	4	1
480	10 "	11	3	2

Allowing, therefore, for the difference between goats and men in the respiratory exchange per unit of body weight, and consequent rate of circulation, it would take about four hours for a man's body to become for practical purposes saturated with nitrogen in compressed air. This conclusion harmonises with the experience of workers in compressed air. Parts in which the circulation is rapid are certainly saturated in a small fraction of this time, as indeed has been shown experimentally by Hill by determining the amount of free nitrogen in urine secreted during rapid diuresis.[1] We think, however, that von Schrötter, who calculated that saturation is nearly reached in man within about twenty minutes, has at any rate made a great *practical* underestimate, both of the time needed for saturation and that needed for desaturation. In making his calculation, he has treated the body as if the circulation through all parts were the same, whereas it differs very greatly in different parts. From the point of view of caisson disease, the quickly saturating parts cause little danger (except with almost instantaneous decompression from very high pressure), as is shown both by the practical experience of men working in compressed air, and by the fact that it is extremely difficult to produce any symptoms in small animals with a rapid circulation rate. It is thus the slowly saturating parts of the body which are of most practical importance. Another source of error is that, as was shown by Dr. Vernon,[2] of Oxford, in connection with our experiments, fat takes up about six times as much free nitrogen as does blood. The body fat thus forms a very large depôt of nitrogen, which greatly increases the time needed for saturation. On sudden decompression of an animal saturated with compressed air the fat becomes blown out with small gas-bubbles.

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[1] *Proceedings of the Royal Society*, vol. lxxix. p. 366, 1907.

[2] *Ibid.*

We are in complete agreement with von Schrötter and Zuntz as to the general form which the saturation curve of any part of the body must of necessity take, assuming the rate of circulation to remain constant (see fig. 1). For instance, a part which takes one hour to become half-saturated will take two hours to become three-fourths saturated, and three hours to become seven-eighths saturated. During desaturation on decompression, if no bubbles have formed to disturb the process, the desaturation curve will be exactly the same.

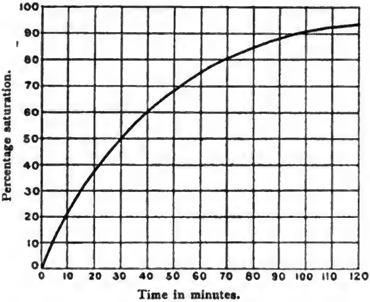

FIG. 1.—Curve showing approximate rate of saturation of parts of the body with an average rate of circulation and percentage of fat.

I now come to another point, as to which we have been led to new and important conclusions. Practical experience of work in compressed air shows that even with very rapid decompression no symptoms of caisson disease ever occur with an absolute pressure of less than 2 atmospheres, and that symptoms are very rare and slight until the pressure rises beyond 2·3 atmospheres, or 19 lb. per square inch. This we found to be true also for goats. Now if it is possible to decompress rapidly and with safety from 2 atmospheres, or a little more, to 1 atmosphere, it seemed likely that it would be possible to decompress with equal safety from 4 atmospheres to 2, or from 6 to 3, since the volume of gas tending to be liberated would be the same in each case. Experiment showed that this was the case, and that the danger of rapid decompression depends, not on the absolute difference between the initial and final pressure, but on the proportion between the two pressures. If this proportion is only 2 or 2·3 to 1, the decompression is safe; if, on the other hand, the proportion is 3 or 4 to 1, the decompression is dangerous. This is illustrated by the experiments in Table IV.

TABLE IV

Absolute Pressure in Atmospheres.	Exposure in Minutes.	Fall of Pressure in Atmospheres.	Relative Reduction of Pressure.	Duration of Decompression in Minutes.	Number of Goats.	Cases of "Bends."	Severe Symptoms.	Death.
6	180	3·4	2·3 to 1	1½	10	0	0	0
4·4	180	3·4	4·4 ,, 1	4	10	3	3	2
4	120	3·4	6·7 ,, 1	6	3	1	1	1
3·6	120	3·0	6 ,, 1	6	4	0	3	0
4	120	3·0	4 ,, 1	1	10	2	4	0

It will be seen that a rapid drop from 6 to 2·6 atmospheres produced no symptoms at all, the fall of pressure being 3·4 atmospheres, and the relation of the higher to the lower pressure being 2·3 to 1. With the same animals decompression from 4·4 atmospheres to 1 produced disastrous effects, the fall of pressure being exactly the same as before, but the relation of the higher to the lower pressure being now 4·4 to 1.

The method hitherto recommended for bringing men safely out of compressed air has been to decompress at a slow and uniform rate. But calculation on the principle already referred to shows that however slow this uniform decompression may be, the difference in partial pressure between the nitrogen dissolved in the tissues and the external air pressure will go on increasing during the decompression. Still more will the proportional difference between the two pressures increase. At the end of the decompression, therefore, the danger, if any, will be at a maximum; whereas during the first half, or more, of decompression time is simply being wasted, or much worse than wasted, if saturation of the body was incomplete, as is nearly always the case in diving. All our experiments confirmed this theoretical deduction.

These considerations led us to introduce a new method—that of decompression in graduated stages. The principle of this method is that the diver or worker in compressed air is brought rapidly to half the absolute pressure (or a little further if his tissues are not saturated), stopped there for a time, then decompressed a little further after sufficient time has elapsed to allow the maximum nitrogen pressure in his tissues to become not more than twice the nitrogen pressure of the air at the lower stage. He is then brought on by further stages on the same principle until he reaches atmospheric pressure. For the difference between the stages a pressure of 0·3 atmosphere was selected, corresponding to 10 ft. (or 3 metres) of sea water. The diver's progress is, of course, controlled by signal from surface, according to the indications of the pressure-gauge on the pump. The proper stoppages, after stays at different depths and for different periods of time, have been carefully calculated and put into the form of a table, which is now in use in the British Navy. A portion of this table is shown in Table V.

TABLE V

Portion of Diving Table for British Navy

Depth.		Total Pressure in Atmospheres.	Time from Surface to beginning of Ascent.	Depth and Duration in Minutes of Stoppages during Ascent.				Total Time for Ascent in Minutes.
Fathoms.	Metres.			12 Metres.	9 Metres.	6 Metres.	3 Metres.	
18–20	33–36½	4·6	Up to 15 min.	—	2	3	7	15
			15–25 „	—	5	5	10	23
			25–35[1] „	—	5	10	15	33
			35–60 „	5	10	15	25	57
			60–120 „	10	20	30	35	97
			Over 120 „	30	35	35	40	142

For ordinary diving work the table limits the stay on the bottom in such a way that the diver can come up safely within half an hour. This is desirable for many reasons: after prolonged stays on the bottom at great depths the time required for safe decompression, even by the stage method, is far too long; and with uniform decompression many hours would certainly be needed at the greatest depths.

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[1] Ordinary limit of time.

The method of stage decompression was very thoroughly tested on goats, and compared with the old method of uniform decompression. The result was to show, we think, beyond all question that the stage decompression method is greatly superior, particularly for diving work. Even when the rate of decompression was much too fast by either method, stage decompression proved considerably safer. The accompanying table (Table VI.) shows a number of results obtained with the same animals and under the same conditions, except that the method of decompression was varied. It should be remarked that in each series, excepting C, the rate of stage decompression was less slow than what was calculated to be required for goats in order to prevent all symptoms, and considerably so in series B, D, and E. The occurrence of a few slight symptoms was therefore expected. It will be seen, however, that deaths and severe symptoms were entirely eliminated by the stage decompression, whereas a number of cases occurred with uniform decompression in the same time, besides a much greater number of slight cases.

TABLE VI

Absolute Pressure 6 Atmospheres

Series.	Exposure in Minutes.	Decompression in Minutes.	Number of Goats.	Stage Decompression.			Uniform Decompression.		
				Cases of "Bends."	Severe Symptoms.	Deaths.	Cases of "Bends."	Severe Symptoms.	Deaths.
A	15	31	35	5	0	0	13	3	1
B	30	31	6	2	0	0	4	1	0
C	30	68	14	0	0	0	7	0	0
D	120	70	13	4	0	0	7	2	0
E	120	92	19	3	1	0	3	5	1
F	180	133	10	2	0	0	5	0	0
Total			97	16	1[1]	0	39	11[2]	2

With goats we found it necessary to provide for parts of the body taking as much as forty-five minutes to become half-saturated or half-desaturated with a given alteration of pressure. For man we therefore considered it necessary to provide for parts requiring seventy-five minutes, as the respiratory exchange per unit of body weight in man is three-fifths that of goats.

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[1] Paralysis of foot lasting 1 hour.

[2] 3 cases of paraplegia, 4 of temporary paralysis, 2 of dyspnœa, and 2 of undefined illness.

A number of experiments in the steel chamber at pressures up to 6½ atmospheres were carried out on men, with stage decompression; and many dives in the sea to pressures of from 4 to 7⅓ atmospheres have also been made by Lieutenant Damant and others, with the time-limits and stage decompression recommended in the new diving tables. No symptom of caisson disease has, however, been observed, so that the new method appears to be practically successful. The old method was to go down and come up slowly at a rate of about 5 ft., or 1½ metres per minute. The accompanying diagrams show the

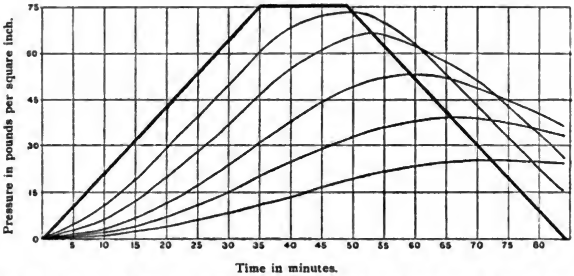

FIG. 2.—Diving to 28 fathoms by old method. The thick line represents the air-pressure. The curves, from above downwards, represent respectively the variations in saturation of parts which half saturate in 5, 10, 20, 40, and 75 minutes.

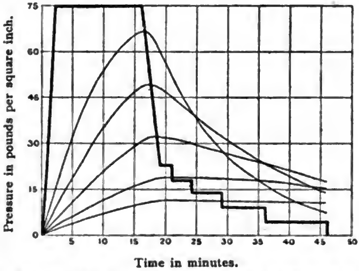

FIG. 3.—Diving to 28 fathoms by new method. The curves, from above downward, represent respectively the variations in saturation of parts of the body which half saturate in 5, 10, 20, 40, and 75 minutes. The thick line represents the air-pressure. Diver 14 minutes on the bottom and 46 minutes under water.

calculated degree of saturation of different parts of the body during a dive to 6 atmospheres pressure for fourteen minutes with the old and the new method. It will be seen at once that the slow descent adds greatly to the danger, while during most of the uniform ascent many parts of the body are actually increasing in saturation; so that by the old method a diver runs a very serious risk of death or paralysis when he reaches surface. By the new method this risk is avoided, and the total time under water is reduced to nearly half. To obtain equally safe results by the method of uniform decompression it would, to judge from the experiments on goats, be necessary to extend the duration of decompression to several hours, the reason being that, in the case of short exposures to high pressure, not only is time wasted during the first half, or two-thirds, of the uniform decompression, but the saturation of most parts of the body continues to increase very seriously, so that at the end the decompression rate is far too fast unless the process is made very slow indeed.

After long exposures to compressed air, as in work in caissons and tunnels at moderate pressures, the saving in time by stage decompression is not so striking; but very substantial gains in convenience become possible. Time, however, forbids me from entering further into this subject, and I must now return to work in mines.

One of the most formidable difficulties met with in the deep mining which is now becoming so common is the great heat which is encountered. It is well known that the deeper we penetrate the earth's crust the higher is the natural temperature of the rock. The rate of increase is usually about 2·5° C. per 100 metres. At some places it is more than this: at others less. At Johannesburg, for instance, the increase is only 0·9° per 100 metres, while in Cornwall it is 3°. At a depth of 1,000 metres, which is now becoming common, the natural rock temperature is usually about equal to the body temperature. The air temperature in a mine may be either above or below the natural rock temperature. Fresh air direct from surface, or the evaporation of moisture, may cause a local reduction in mine temperature. On the other hand the slow oxidation of mineral substances, such as iron pyrites (FeS_2), very commonly causes the mine temperature to rise considerably above the original rock temperature. Miners are thus much exposed to excessive heat, and the influence of this on their working powers and health is a matter of great practical importance.

In some of the mines of Cornwall the heat is probably as trying as in any place where men have to live and work; and my observations there led me to make experiments on a man's power of remaining in and working in warm air. It is of course well known that men can remain for a short time in extremely hot air, if it is dry. A temperature of 100° C. in a Turkish bath, or even a much higher temperature, can easily be borne for a few minutes; but there is surprisingly little information as to what temperature a man can continue to withstand for hours at a time during his ordinary occupation. My observations were made on several persons, partly in mines and partly in artificially heated rooms.[1]

One main result was that in still air, during rest, and with the subject of the experiment stripped to the waist, the maximum temperature which could be borne for several hours without marked pathological symptoms was 31° to 32° C. (88° to 90° F.) by the *wet-bulb* thermometer. Neither the actual temperature by the dry-bulb thermometer, nor the degree of humidity, nor the percentage of moisture in the air, mattered by itself. The determining factor was simply the wet-bulb temperature. If this exceeded 31° to 32° (the actual critical point seemed to vary slightly in different individuals), the body temperature began to rise steadily. The accompanying diagram shows the results of several experiments made on myself.

It was somewhat remarkable that when the air temperature was just above the critical point, the rise of body temperature did not slacken or cease as the difference between body temperature and wet-bulb air temperature began to increase. Actually the rate of rise of body temperature seemed to increase rather than diminish. The reason for this is the fact, clearly proved in some quite recent experiments by Dr. Sutton, of Oxford University, that the respiratory exchange, and consequently the heat production in the body, rises very markedly with even a slight increase in the rectal temperature. Hence the heat-loss cannot catch up the heat-production, and the body is in a "vicious circle."

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[1] Details of part of these experiments will be found in the *Journal of Hygiene*, vol. v. p. 494.

A rise of 2° C. over the normal day body temperature was sufficient to produce much discomfort—a rapid pulse rate, and marked dyspnœa on exertion. A greater rise than this produced alarming symptoms when any considerable exertion was made, as in climbing ladders underground.

In a good air current the critical wet-bulb temperature was found to be about 2° C. higher. During work, on the other hand, the critical wet-bulb temperature was considerably lower—about 26° to 27° with fairly hard work in still air.

That the wet-bulb temperatures should be the determining factor is exactly what might have been predicted on physical grounds; and as the body, unlike the wet-bulb of a thermometer, is itself a source of heat, it is equally intelligible that moving air raises the critical wet-bulb temperature, and increased heat-production in the body lowers it.

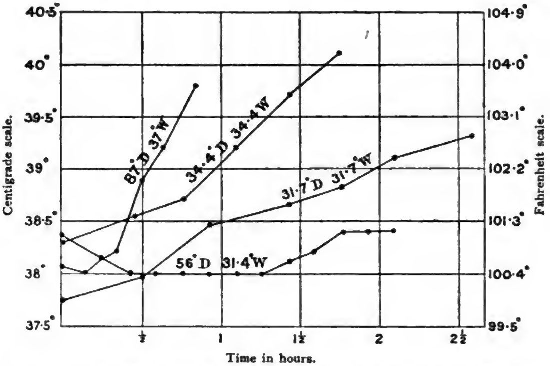

FIG. 4.—Variations of rectal temperature during rest, stripped to the waist, at various air-temperatures.

D = dry-bulb air-temperature. W = wet-bulb air-temperature.

A further point brought out strikingly in some of the experiments was that the sweating produced by heat depends primarily on the skin temperature, and not on the internal temperature of the body. There is quite commonly a fall in the rectal temperature at the time when most profuse sweating breaks out on going into warm air. On the other hand, sweating does not occur in hot air until the skin temperature reaches a certain point. If the skin is cold to begin with it may be half an hour or more before sweating breaks out in a very warm room, whereas there will be profuse sweating within a minute if the skin is warm to start with.

I found that the Cornish miners were frequently employed in places where the wet-bulb temperature was from 30° to 38°. It might be supposed that, under such circumstances, cases of heat-apoplexy would be common; but I never could hear of any such cases, nor did I find, even in the hottest places, that the men allowed their temperatures to rise more than very slightly. What they did was simply to come out and rest in a cool place as soon as they felt that they were getting too hot. In fact, they seemed to be nearly always resting in this way. At a wet-bulb temperature of about 27° the amount of work done by a miner begins to fall off, and as the wet-bulb temperature rises further the work done gradually diminishes to a vanishing point. It may be that a miner's health sometimes suffers from the heat; but I could not find any clear evidence of this, and the men working in hot mines seem to be usually quite healthy. What undoubtedly suffers very heavily is the pocket of the mine-owner.

On the other hand, mine-horses often die of heat-apoplexy; and so fatal is the heat to horses that their employment is avoided in some of the hotter mines. They are liable to be worked too hard in a warm mine, just as soldiers are liable to be overmarched in hot weather; whereas the miners, who are perfectly free to follow the promptings of nature—for instance, to take off their clothes, stop working, or go into a cool place, or even into cool water, when they are too hot—escape without harm.

It seems clear that, for the economical working of a mine, the wet-bulb temperature should not in general be allowed to rise beyond about 27°—unless, perhaps, where there is a good air-current. To maintain this limit in the ordinary working places does not seem to be very difficult, provided the right measures are taken in laying out the ventilation. This matter will soon have to be studied much more closely by mining engineers than has been the case hitherto.

I should like, in conclusion, to point a moral, if I may, in connection with the hygienic regulation of engineering and manufacturing work. No one doubts that the health, efficiency, and comfort of our working population are matters of the utmost importance. But the desirability of properly investigating the hygienic conditions of various industries is scarcely yet recognised as it ought to be. There is plenty of talk and a large number of regulations; but real knowledge—the indispensable basis of effective action—is too often lacking, and can be gained in no other way than by careful and detailed observation and experiment. This can be illustrated from all branches of hygiene—for instance, by the immensely important knowledge patiently gained during the last few years as to the nature and means of spread of various infective diseases.

I wish, however, to emphasise the same fact in connection with industrial hygiene; and perhaps the specific problems just discussed may enable me to do so. They concern the physical and chemical characters of the air in its relation to certain industrial employments. Insufficient study has, in spite of the best intentions, led to many mistakes in connection with these employments. First, as regards work in compressed air, we find on the one hand that divers have been more or less hampered or endangered by that somewhat rare condition, poisoning by carbon dioxide. But if we turn to men employed in compressed air in tunnels, etc., we also find the conditions—in England at least—reversed in a curious way. It has become a common popular belief that, provided the carbon dioxide percentage is low enough, all must be well with any kind of air. For instance, in the case of the large tunnel at present being constructed in compressed air under the Thames at Rotherhithe, London, the County Council, regardless of the enormous expense, has prescribed that, in view of the danger of caisson disease, the proportion of CO_2 shall not exceed that in the average air outside by more than 4 volumes per 10,000. It is, of course, not conceivable that by increasing the air supply to such an extent caisson disease can be prevented. The chief effect of the large air supply seems to be that the tunnel is very warm, as in consequence of the large quantity of air it is not effectively cooled between the compressors and the tunnel. The large air supply is thus probably doing more harm than good; and the absence of effective regulations for preventing caisson disease lays the County Council open to criticism in view of the long-existing knowledge of the subject.

Again, the well-intentioned regulation hitherto in force in the British, German, and other navies, that a diver should always descend very slowly, has probably cost many a diver his life.

To turn to the mining industry, one finds that often no expense is spared, and burdensome regulations may be imposed by law, in the endeavour to cure by unsuitable means evils for which a little real investigation would have shown an effective cure. In the Cornish mines, for instance, more ventilation was being provided as a remedy for the evils caused actually by stone dust and ankylostomiasis. The increased ventilation was apparently only aggravating the evil by making the working places drier and more dusty, just as in coal mines increased ventilation has, by itself, often increased the danger of colliery explosions by making the coal dust drier. Courrières Colliery, where 1,100 men were killed by a coal-dust explosion last year, was probably one of the best-ventilated mines in Europe.

As regards heat and moisture in the air, we have in England the curious anomaly in our Factory Act that the wet-bulb temperature in cotton factories, where women are employed all day, is expressly permitted by law to rise to even 37°, provided that the proportion of CO_2 does not exceed 9 volumes per 10,000! I do not for a moment mean to imply that any manufacturer would permit such a state of matters to exist in his factory, or that the workers would stay for an hour in such an impossible atmosphere; but the extemely well-meant English regulations as to temperature and humidity in the air of factories furnish one instance out of many, illustrating the need for more knowledge and investigation.

Such knowledge must be gained to a large extent on the spot, and not merely in a laboratory. Men who are tied to their work in a laboratory are often called upon to express opinions about matters of industrial hygiene without having any adequate opportunity of personally investigating the actual conditions. It is almost invariably the case, however, that investigations on the spot are essential, and that discussion with engineers, managers, and workmen throws entirely new light on the subject-matter. For one thing, the engineers and managers help us, beyond everything, to think of things quantitively and in their relations to other things. This lesson is one which is often greatly needed in our branch of science. In spite of the inspiring examples of such men as Pettenrofer or Paul Bert or Parkes, we seem constantly in danger of forgetting it. We should progress hand in hand with the development of each industry, and be ever ready to help the engineer or manufacturer. It is only by doing this on the one hand, and by keeping in close and living touch with physiology and pathology on the other, that industrial hygiene can properly fulfil the very important duties which human progress has assigned to it.

THE GREAT SCANDINAVIAN OVERTHRUST

By J. W. GREGORY, F.R.S.
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Scandinavia and Scotland are geologically nearly akin, and some of the difficult problems of Scottish geology may be solved by the Scandinavian evidence, which is often bolder and simpler.

The two lands were originally both part of the old Continent of Arctis; and they both have a similar foundation of crystalline schists and gneisses, which in Scandinavia are accepted as Archean. In both countries the older rocks are covered by wide sheets of pre-Cambrian sandstones—the Torridonian of Scotland and the Algonkian series of Scandinavia. Both countries have fossiliferous Cambrian rocks along their north-western edge, with a wider development of Lower Palæozoic, and even younger sediments to the south-east of the crystalline mass. That the schists of Scotland were once connected with those of Scandinavia is suggested by their frequent coincidence in strike, indicating that the structural grain of the countries was continuous across the North Sea. The geological connection has, however, often been geographically broken, and the direct land bridge apparently existed last in Pliocene times.

The student of crystalline schists in Scandinavia has the advantage over the Scotch geologist of the presence, in many localities, of fossiliferous Lower Palæozoic rocks in close association with the schists. In the Scottish Highlands, on the other hand, the fossiliferous rocks are restricted to a band along the north-western edge, except for a couple of localities containing doubtful worm tubes. The structure of Scotland, in its turn, helps to elucidate that of Scandinavia; for it was research on Scottish geology that explained the occurrence of fossiliferous sedimentary rocks beneath series of crystalline schists and gneisses. Murchison attributed this

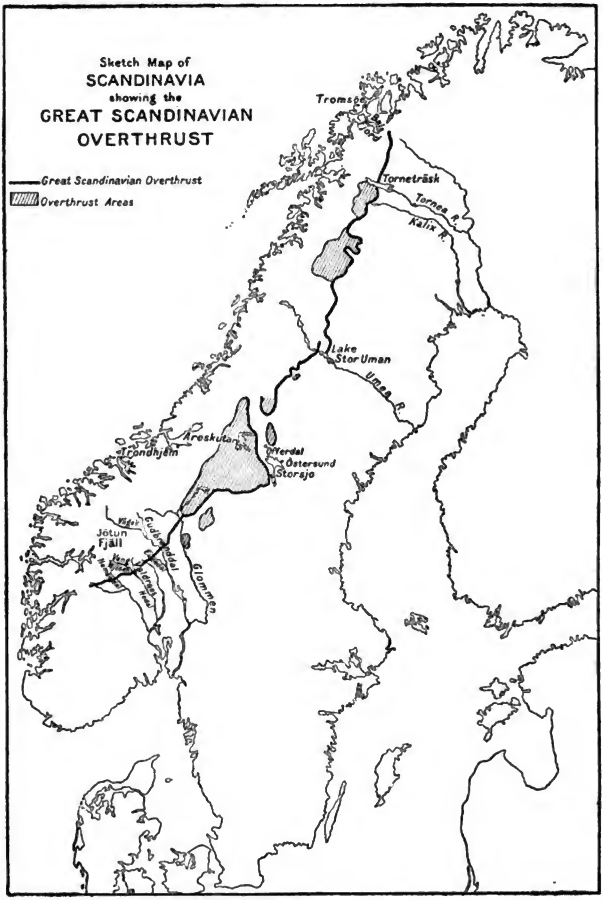
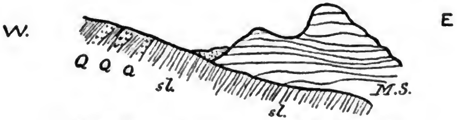


FIG. 1.

[The Valdraes is the valley marked above the name.]

arrangement, in the case of the Scottish Highlands, to selective metamorphism having converted the upper beds into schists, while leaving the lower beds unaltered. This view was also adopted in Scandinavia. It assumed, in accordance with the law of superposition, that the overlying beds must be the younger, and the chemical difficulties of selective metamorphism were left for subsequent explanation. That these difficulties were great was evident in Scandinavia from the observations made by Gumaelius in Offerdal during 1869. He then showed, in a section reproduced as fig. 2, the existence of a block of mica schist overlying phyllites or clay slates, with relations which selective metamorphism could hardly explain.[1]

Murchison's theory was overthrown in Scotland by the discovery that the crystalline schists had been thrust into positions where they appear to rest conformably on younger beds. And the same explanation has been demonstrated in Scandinavia, although there it appeared at first almost incredible owing to the vast scale of the phenomena.



Q = Quartzite. sl = slate. M.S. = Mica Schist.

FIG. 2.—Section in Offerdal by Gumaelius.

The literature of the Scandinavian overthrust is somewhat scattered, and it is mostly written in Swedish or Norwegian. Hence a brief statement of some conclusions and reference to the original authorities may be of value to British geologists. It has recently been my privilege to examine one of the typical overthrust sections on the shores of Lake Torneträsk in Swedish Lapland. For directions and kind help in this visit, and for showing me the material bearing on this question in the museums at Stockholm and Upsala, I owe my warmest thanks to Prof. Högbom of Upsala, Dr. Gunnar Anderson, Director of the Geological Survey of Sweden, and Dr. Holmquist, of the Technical High School of Stockholm. Nor must I omit mention of my indebtedness to the writings of Herr A. E. Törnebohm, late Director of the Geological Survey of Sweden, to whose work the present interpretation of the complex mountain structure of the High Fells of Scandinavia is so largely due.

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[1] This section was referred to by Törnebohm in 1873, *Sver. Geol. Unders. Ajhandl.* No. 9, p. 42; but it apparently remained in manuscript until it was published by Högbom in 1894.

Scandinavia consists geologically of a foundation of Archean and pre-Cambrian rocks, which are exposed over nearly all Eastern and Southern Sweden; they also form the fringe of islands along the Atlantic coast and most of the rugged southern provinces of Norway between Christiania and Bergen. The second important constituent is a band of schists and gneisses, which forms the mountain axis of Scandinavia, parallel to the Atlantic coast. It was doubtless once part of an old fold-mountain chain, which has now been cut down into a dissected pene-plane, wherein the existing ridges are independent of the heights formed by the original folds. The schists of this region are associated with thick masses of sandstone and conglomerate—the sparagmites and Dala Sandstone. Some of these rocks were once believed, as by Murchison, to be Old Red Sandstone; but they are now generally recognised as of pre-Cambrian age, and accepted as members of the Algonkian system. The schist belt also includes some fossiliferous rocks; and it has been held that the schists themselves are only Palæozoic sediments that have undergone thorough alteration. They were divided by Törnebohm in 1872 into two series, a lower or Seve Group, and an upper or Köli Group, and both were then regarded as Silurian or even post-Silurian.[1]

In addition to these rocks, which are doubtfully assigned to the Palæozoic, there are some slightly altered, sedimentary rocks, many of which are fossiliferous, so that their age is known. These rocks include representatives of the four oldest Palæozoic systems. Here and there from Lapland to south-western Scandinavia are areas of coarse sandstones, which are regarded as probably Devonian. The Lower Palæozoic rocks include members of the Silurian, Ordovician, and Cambrian; and their classification is somewhat complex, as they are developed with two very different facies—the eastern and the western.

The eastern facies includes normal sedimentary rocks, of which the upper members are shown by their fossils to include representatives of the Silurian and Ordovician systems; while beneath the fossiliferous rocks there are beds of alum shale and sandstone which, from their stratigraphical position, are referred to the Cambrian. These eastern rocks are but little altered, and they occur in simple regular sequence, with abundant limestones and fossils.

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[1] A. E. Törnebohm, "En geognostisk profil öfver den skandinaviska fjällryggen mellan Österund och Levanger," *Öfver K. Svens. Vet. Akad.* 1872; also *Sver. Geol. Unders. Afhandl.* Ser. C, No. 6.

The Lower Palæozoic rocks of the western facies are lithologically strikingly unlike those assigned to the same age in districts farther to the east. The great bulk of the western rocks are schists; there are but few limestones, and fossils are found only in isolated deposits, which range in age from the Lower Cambrian to the Silurian. The striking lithological differences between the eastern and western rocks is explained as being partly due to more intense metamorphism in the western area; but this explanation is not alone adequate, as the rocks when first deposited must have been essentially different in composition in the two areas. It is therefore further explained that the "Silurian" rocks of the western area are due in part to extensive eruptions of basic rocks, while sediments were quietly accumulating in the seas to the east.

The Lower Palæozoic rocks of the western facies are themselves subdivided into the eastern and western sub-facies; their relations are somewhat uncertain, and the settlement of this question will be watched with much interest by Scotch geologists, from its analogy to some doubtful points in the correlation of the schists of the Southern Highlands of Scotland. Both the eastern and western sub-facies consist of series of phyllites, clay slates, schists, and gneisses, of which the most highly crystalline rocks belong to the lower division of the eastern sub-facies.

The rocks vary in metamorphism along their strike; though why the most highly metamorphosed areas are distributed as shown in Törnebohm's map is not obvious. Thus the Sul Schists extend from north-north-east to south-south-west in a narrow band 2 miles wide and 80 miles long; and it is marked as strongly metamorphosed for a length of about 22 miles; whereas the adjacent parallel band of the Meraker and Selbu Schists is strongly metamorphosed for 45 miles farther to the south-south-west. In both sub-facies there are some fossiliferous beds: namely, the Höilandets group of Trinucleus Sandstone age (Ordovician) in the western series, about 25 miles south-south-west from Trondhjem; and the Sul slates, containing graptolites belonging to the lower part of the true Silurian, in the eastern series. These fossiliferous beds are held to support the view that the schists of the area are altered Lower Palæozoic rocks. This, however, is the one conclusion in Scandinavian geology which foreign geologists may be most excused if they hesitate to accept, until further evidence has been published that the fossiliferous beds cannot be younger rocks folded or faulted in among older schists. The solution which Prof. Bonney gave of the same problem in the Lepontine Alps may be applicable to the schists of the Trondhjem district.

The belief that these schists were all Silurian was, however, naturally adopted at first, because unaltered fossiliferous Lower Palæozoic rocks are found in places beneath wide sheets of schist and gneiss. It therefore appeared necessary to accept the upper beds as the younger in age. But it has been proved that, as in Scotland and the Alps, the superposition of the schists is due to earth movements. And in Scandinavia the overthrusting has taken place on a scale greater than has been established in any other part of the world.

The development of these views may be seen from the successive explanations of the geology of Åreskutan in Jemtland, one of the best known Swedish mountains (4,645 ft.). The lower eastern and western slopes of this mountain consist of the normal Lower Palæozoic rocks of the eastern facies; they include the Cambrian alum shales, above which are more shales, and the Pentamerus Limestone of the base of the true Silurian. The whole of the upper part of the mountain consists of crystalline schists of the Seve Group; they include hornblende schist, mica schist, crystalline limestone, and garnetiferous gneiss. The base of the crystalline schists is a quartzite or quartz-schist, which is in places a conglomerate. "The contact between this quartzite and the Silurian clay rocks I saw laid bare," says Törnebohm,[1] "in a small stream that descends from the western side of Åreskutan. The dip is here not more than 15° or 20° to the east, and the superposition is very clear. The boundary between both formations stands out very definitely, yet without any marked discordance. Over the quartzite, which is not very thick, follow first hornblende schists, which alternate with mica and quartzitic schists, and include some small layers, only a few inches thick, of white crystalline limestone; further up come a somewhat thick quartzite schist, wherein occur the copper ores of Åreskutan; and then follow gneiss-like rocks (which sometimes include hornblende and sometimes garnets as accessory constituents), and they, with alternations of hornblende and mica schists, extend up to the summit of the mountain."

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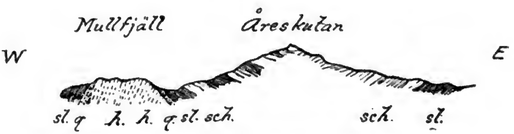
[1] Törnebohm, *Afhandl. Sver. Geol. Unders.* No. 9, 1873, p. 41.

The same sequence is exposed on the eastern side of the mountain, and Törnebohm therefore naturally concluded that "the schists of the Seve Group, in spite of their crystalline structure and their primæval aspect, are younger than the surrounding Silurian deposits, and that between them occurs a definite geological boundary which is sometimes marked by beds of conglomerate."[1]

This conclusion is represented in a section across Åreskutan which is reproduced as fig. 3. Ten years later Törnebohm recognised that the superposition could not be trusted, as the relations of the Dala Sandstone (now recognised as Algonkian) had been in places inverted by overthrusting; but he still accepted the view that the Seve Group, with the Vemdal quartzite which he regarded as its base, is later than the underlying Lower Palæozoic rocks, and supported this conclusion by fresh evidence from the district of Herjedalen.[2]



h = halleflinta.
q = quartzite. (Cambrian.)
sch = schist. (Seve Group.)
sl = slate with limestone. (Silurian.)

FIG. 3.—Section through Åreskutan after Torneböhm, 1872, representing the Are schists as post-Silurian.

The demonstration by Prof. Lapworth and by Dr. Horn, Dr. Peach and their colleagues of the Scottish Geological Survey, that the superposition of schists over normal sediments in the north-west Highlands of Scotland was due to overthrusting, encouraged Törnebohm to believe that the same process was the cause of the perplexities of mountain structure in

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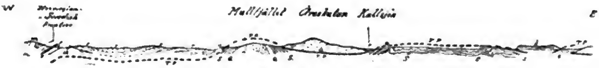
[1] Törnebohm, *Afhandl. Sver. Geol. Unders.* No. 9, 1873, p. 42.

[2] A. E. Törnebohm, "Om Vemdalsqvartsiten och öfriga qvartzitiska bildningar i Sveriges sydliga fjälltrakter," *Geol. För. Förh.* vol. vi. (1883), pp. 274-94. pl. xii. and xiii.

Scandinavia. In 1888 he redescribed the geology of Åreskutan,[1] and identified the schists and gneisses of the summit of the mountain as pre-Silurian rocks, pushed from the west over the lower but younger Palæozoic sediments. This view is represented in fig. 4 from Törnebohm's memoir of 1896.

In 1891 Törnebohm explained other cases of the apparent interstratification of slates and quartzites with gneisses as due to inversion by folding. Thus on the northern foot of the Jötun-Fjäll in Norway, on the southern shores of Lake Våge, the apparent sequence consists of the following beds, all of which are dipping southwards: (5) upper gneiss, (4) upper quartzite, (3) clay slate, (2) lower quartzite, (1) lower gneiss. Törnebohm explained this arrangement as due to an isoclinal, by which the quartzite and gneiss are repeated on both sides of the slates.[2] According to this interpretation there are only three beds, and the gneiss is the oldest.



S = Silurian.
Q = Quartzite.
m = Meraker Schists.
r = Röros Schists.
å = Åre Schists.
T.P. = Thrust Plane.

FIG. 4.—Section through Åreskutan after Torneböhm, 1896, showing the Åre schists as pre-Silurian.

This conclusion was, however, rejected by Björlykke, who in 1894 accepted the fact that much of the so-called Mountain Quartzite (*Höifjeldskvartsen*) of the Norwegian Fells was a gneiss and not a quartzite; and he claimed that this gneiss was of post-Ordovician age, and that the crystalline rock had been originally deposited unconformably on the unaltered, older Ordovician beds.[3]

In 1905 Björlykke issued as No. 39 of the *Norges Geologiska Undersögelse* a work on the mountain structure of Central Norway, in which he maintains that the upper sparagmite group is of Devonian age, and that, for that area, "the theory of overthrusting must be abandoned." For the geology of

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[1] A. E. Törnebohm, "Om fjällproblemet," *Geol. För. Förh.* vol. x. (1888), pp. 328–36.

[2] A. E. Törnebohm, "Om högfjällsqvartsiten," *Geol. För. Förh.* vol. xiii. (1891), p. 41.

[3] K. O. Björlykke, "Höifjeldskvartsens nordostligste udbredelse," *Norges Geo., Undersög.* No. 14; Aarbog for 1892 og 1893 (1894) pp. 64, 73, 74.

Mount Åreskutan he apparently accepts the suggestion of Reusch, that its upper gneisses are altered eruptive rocks. From the same memoir it appears that Schiötz, in 1902, accepted the action of overthrusts to explain the structure of Österdal in Eastern Norway.

In 1894 Herr Törnebohm's views received the powerful support of Prof. Högbom, now of the University of Upsala, who demonstrated the truth of the overthrust theory by careful mapping of the High Fells of Jemtland. His results were published in a monograph,[1] and illustrated by a geological map of the province on the scale of 1 to 500,000. His survey proved that the overthrusting has taken place on a scale even greater than in Scotland. Two years later followed Dr. Törnebohm's important memoir,[2] which described the geological structure of the main High Fells both of Norway and Sweden, and extended the overthrust explanation to the districts to the south-west of Jemtland.

The surveys of Törnebohm and Högbom leave no doubt as to the occurrence of a great overthrust of pre-Cambrian schists over Lower Palæozoic sediments. The main overthrust mass covers an area of some 5,200 square miles; this vast sheet of rock was thrust from west to east over the underlying fossiliferous sediments. The evidence is clearest in the case of some outliers of the schists, which have been cut off by denudation from the main overthrust mass. The best known of these outliers are at Offerdal, a locality to the north-west of Östersund and thirty miles east of Åreskutan. Offerdal is a valley running from north-west to south-east and containing the upper arm of Lake Nälden. The floor of the valley is occupied by the true Silurian beds, which are thrown into many small folds, and are often isoclinals dipping to the west (fig. 5). The valley is bounded to the north by a plateau, which is cut through by the valley of Lake Landösjön; the plateau and the area to the north of that lake are formed by overthrust mica schists and crushed Algonkian conglomerates and quartzites. The southern side of the Offerdal valley is formed by a block mountain known as Alsen, which is built of the same rocks.

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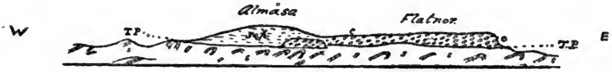
[1] A. G. Högbom, "Geologisk Beskrifning öfver Jemtlands Län," *Sver. Geol. Unders. Afhandl.* Ser. C, No. 140 (1894), 107, p. 1, pl. and map.

[2] A. E. Törnebohm, "Grunddragen af det Centrala Skandinaviens Bergbyggnad," *Handl. K. Svens. Vet. Akad.* vol. xxviii. No. 5 (1896), 210 pp. 4 pl. and geological map of Central Scandinavia, on scale of 1 to 800,000 (with German Summary pp. 179–97).

According to Prof. Högbom's map, the Pentamerus Limestone (*i.e.* Silurian of the Llandovery Series) can be traced all round the foot of the Alsen outlier; and looking across Offerdal to the north, the superposition of the schists above the limestones is shown in a section, reproduced as fig. 5.

The maps and sections of both Törnebohm and Högbom appear convincing that the only satisfactory explanation of the facts is that the schists have been overthrust above the Lower Palæozoic sediments.

From Jemtland, the overthrust has been traced south-west into Norway and northward into Lapland. The evidence in the far north has been collected by several observers, including Törnebohm, Högbom, Holmquist, Sjögren, and Svenonius.[1] Prof. Sjögren[2] has described the sections around Sulitelma, and Dr. Holmquist[3] the wide area of schists thrust over sediments assigned to the Silurian, to the south-east of Sulitelma and south-west of Qvikkjokk. To Dr. Holmquist[4] is also due the most detailed account of the overthrust area to the south of Torneträsk, the most northern of the great Swedish lakes. The evidence at Torneträsk is very clear, and, by the kindness of Herr H. Lundbohm of Kiruna and the Traffic Manager of



s Contorted Silurian (chiefly Upper Silurian).
sch Schists. (Seve Group.)
c = Crushed Sparagmite.
T.P. = Thrust Plane.

FIG. 5.—The north bank of Offerdal, after Högbom.

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[1] A bibliography has been recently given by Högbom, Nörrland, 1907, pp. 108–9.

[2] H. Sjögren, "Om Sulitelma-områdets bergarter och tektonik," *Geol. För. Förh.* vol. xviii. (1896), p. 346.

[3] P. J. Holmquist, "En geologisk profil öfver Fjellområdena emellan Kvikkjokk och Norska Kusten," *Sver. Geol. Unders. Afhandl.* Ser. C, No. 185 (1900), 100 pp. 2 pl.

[4] P. J. Holmquist, "En geologisk profil öfver den skandinaviska fjällkedjan vid Torneträsk," *Geol. För. Förh.* vol. xxv. (1903), pp. 27–78, pl. i.–iii. And "Bihang till Törneträskprofilen," *ibid.* pp. 373–90, pl. xii.

the Lapland Railway, I was enabled to spend a few hours at Kaisepakte, where the thrust plane is most accessible.[1]

A bluff of rock here rises steeply above the southern shore of the lake; the lower part of the slope consists of a massive pink granite. Then follows a series of brown nodular shales, with some layers of conglomerate; next a green shale and a brown nodular shale with some concretions; then follows a bed of dark blue massive quartzite. The shales are normal sedimentary rocks resembling in aspect some of our Tarannon shales. A fossil has been found in them at Luopahta, a few miles farther to the east. Holmquist[2] quotes an opinion based on it that the beds are of the age of the Chasmops Limestone (Middle Ordovician); but the fossil appears to be indeterminable, though its presence encourages the hope that better material will reward further search. Above these Lower Palæozoic sediments comes a sheet of cataclastic schists, some of which still retain the characters of augen-gneiss; but the main mass of rock has been broken down into a mylonite. This shattered rock has been named "Kakarit" by Svenonius. All stages of mylonitisation may be seen, including crushed gneiss, banded felspathic quartzite, and banded granulites; the extreme stage in the dynamo-metamorphism is reached in some fine-grained pseudo-phyllites, which look like simple slates.

The overthrust rocks are intensely crushed and contorted, great blocks being composed of layers twisted into complex folds and overfolds. The underlying sediments, on the other hand, often remain horizontal or with a dip of only 2°. Examination of this section is convincing that the crystalline rocks that form the bluff of Kaisepakte have been thrust over the unaltered, undisturbed underlying sediments. The descriptions by Dr. Holmquist of the adjacent districts to the south of Torneträsk; by Törnebohm[3] of the country to the north of the lake at the head of Balsfjord, to the south-east of Tromsöe; by Sjögren of Sulitelma; and by Holmquist of the country south of Sulitelma, show that this overthrust traverses the whole length of Norrbotten, the northernmost province of Sweden.

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[1] During my visit I had the benefit of the company of Herr Ljüstrom and Herr Sundius of Upsala.

[2] Holmquist, *Geol. För. Förh.* vol. xxv. p. 38.

[3] A. E. Torneböhm, "Om formationsgrupperna inom det nordligaste Skandinavien," *Geol. För. Förh.* vol. xxiii. pp. 206–17.

There is also evidence of the overthrusting across Westerbotten, between Norrbotten and Jemtland. The overthrust can indeed be traced from 69° N. lat. in Norwegian Lapland across seven degrees of latitude in Sweden, till the line recrosses the frontier and continues for 150 miles farther into Norway. Its course in Southern Norway was traced by Törnebohm across the valleys of the Glommen, of Gudbrandsdal, Espedal, the Valdres valley (Hedal), and Hemsedal. His conclusions were supported by Reusch's[1] description of the country around Vangs Mjösen and Slidre, in the upper part of the Valdres Valley, where the Archean granites are overthrust over phyllites and quartzites assigned to the Cambro-Silurian. And the course of the great overthrust has been continued westward round the Sognefjällen to the Hardangerfiord, by the work of Reusch, Rekstad, and Björlykke,[2] and by Rekstad in the Hemsedalfjällen.[3]

The Scandinavian overthrust is therefore on a colossal scale. It follows the main mountain chain of Scandinavia throughout its entire length. Its length, according to Törnebohm, is about 1,800 kilometres (over 1,100 miles). It is therefore on a much larger scale than in Scotland, where the length of the overthrust from Glenelg to its northern end at Whitten Head is about 100 miles. The width of the overthrust is even more startling. Törnebohm claims that the overthrust masses, which are still 1,500 metres thick, have travelled eastward for a distance of eighty miles. He remarks that "such an immense width is something never yet precedented in the annals of geology, and he does not conceal from himself the fact that its possibility will be generally doubted. But after many years of investigations he has come to the conviction that only by such a great overthrusting can the actual relations be explained; so he is not afraid to express this conviction boldly." Törnebohm claims that the width of the overthrust is not disproportionate to its length. The demand made on the strength of the rocks is, however, at first staggering; so it is not surprising that the development of the overthrust hypothesis in Scandinavia met with some opposition.

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[1] Hans Reusch, "Höifjeldet mellem Vangsmjösen og Tisleia (Valdres)," *Norges Geol. Undersög.* No. 32; Aarbog for 1900, pp. 45–88.

[2] "Fra Hardangervidden," *Norges Geol. Undersög.* Aarbog for 1902, No. 2.

[3] *Ibid.* 1903. The south-western extension of the overthrust has been described by Törnebohm, "Om den skandinaviska fjällkedjans sydveständе," *Geol. För. Förh.* vol. xxv. (1903), pp. 282–8.

The criticisms have followed three main lines. (1) The post-Silurian age of the schists and gneisses overlying the sediments is still maintained by several Scandinavian geologists. (2) The superposition of the older beds has been attributed by Svenonius to complex overfolding; he explained the succession of the rocks in Norrbotten by contortions similar to those formerly introduced in Swiss geology (fig. 6, after Svenonius). (3) The invocation of numerous overthrusts instead of one vast movement.

The third hypothesis has been advanced by Dr. Holmquist, from the evidence collected in his careful study of the districts to the south of Torneträsk. He holds that instead of there having been one vast overthrust, which in that area would have to be thirty-five miles or more in width, there have been many shorter overthrusts. The "Silurian" rocks have been thus sandwiched between the crystalline rocks; and, according to Dr. Holmquist, the tops of the folds sometimes expand laterally beyond their impressed limbs, like an exaggerated Alpine fan. But these sections have been ridiculed as "mushroom constructions" by Törnebohm, who holds to his faith in one great movement.[2] Dr. Holmquist's view, however, appears to be possible, and it has the recommendation of making less trying demands on the strength of the rocks. The overthrust rock-masses are comparatively thin in proportion to their extent, and it would appear very doubtful whether they could have been thrust forward in a slab by pressure applied thirty miles behind in the case of Lapland and eighty miles distant in Jemtland. We are forbidden to appeal

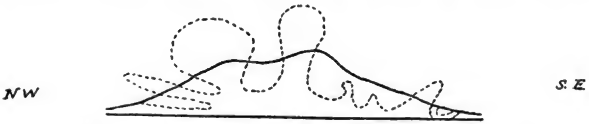

FIG. 6.—Section through Daunevarra, Lapland (after Svenonius, 1896).

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[1] F. Svenonius, "Om Berggrunden i Norrbottens Län," *Sver. Geol. Undersok. Ajhandl.* Ser. C, No. 126, 1892, pp. 37–41, and "Några Bidrag till belysning af eruptivens betydelse för fjällbildningarna," *Sver. Geol. Unders. Afhandl.* Ser. C, No. 161 (1896), pl. 1.

[2] A. E. Törnebohm, "Om Torneträsk-profilenstydning," *Geol. För. Förh.* vol. xxv. (1903), pp. 83–92.

to a very thick overlying rock cover, or the underlying shales must have been more disturbed. The process must have happened in the fracture zone of the crust and not in the deeper zone of fluxion. Hence if Dr. Holmquist's view be found correct, and could be extended by further mapping to Jemtland, it would simplify the explanation of the crustal movements, and would still leave the Scandinavian overthrust the greatest yet discovered.

The Scottish and Scandinavian overthrusts are accompanied by many of the same phenomena. The most significant difference is that the movements took place in opposite directions; in Scotland the rocks above the thrust planes were pushed westward; in Scandinavia they travelled eastward. The disturbances were therefore doubtless due to changes in the land that occupied the area between the Scandinavian High Fells and the North-West Highlands of Scotland. The thrusts, on both sides, were outwards towards the depressions that probably existed in the Baltic region and off the western coast of Scotland.

Supplementary Note on the Literature

In addition to the literature cited in the text reference may be made to the following. Full bibliographies of the earlier literature are given by Törnebohm in his *Grunddragen*, 1896, pp. 202–5, and by Högbom in his Monograph on Jemtland, 1894, pp. 100–3.

A short summary of the literature on the investigations of 1868–71 is given by Törnebohm, "Till historiken öfver de geologiska undersökningarna i Sveriges fjälltrakter," *Geol. Fören. Förhandl.* vol. vii. 1885, pp. 669–73.

A summary is given by Prof. Högbom in the third section of his paper, "Sur la tectonique et l'Orographie de la Scandinavie," *Annales Géogr.* vol. xi. 1902, pp. 122–33, pl. v.

The course of the overthrust line in Sweden is marked on the geological map of Sweden on the scale of 1 to 1,500,000, issued by the Swedish Geological Survey in 1901.

Many of the memoirs quoted from the *Afhandlingar* of the Geological Survey of Sweden were also published in the *Förhandlingar* of the Geological Society of Stockholm.

THE REPAIR OF A NERVE

By W. D. HALLIBURTON, M.D., F.R.S.

It is not probable that many readers of Science Progress have ever experienced the misfortune of having an important nerve cut across. But those engaged in hospital practice, especially in manufacturing districts where machinery is employed, often see accidents of this nature. The result of such an injury is that the parts of the body which the divided nerve served to link with the central nervous system are destitute of the power to move and to feel. The telegraphic service of the body has been interfered with, and the brain is no longer able to transmit its commands to the motor mechanism, nor to receive communications from that part of the sensory surface which is severed from it by the division of nerve fibres. Many of these cases recover after the lapse of time, and this period can always be shortened if by surgical interference the divided segments of the nerve are sutured together.

If, on the other hand, the injury occurs in the central nervous system, the effects are more serious. Suppose, for example, the spinal cord is divided or crushed, then the main line of communication is no longer capable of conducting nerve impulses up and down, and a large area of the body surface is thrown out of connection with the sensorium. And again, unless the division is a complete one, a certain amount of recovery takes place. But the method of repair is different in this case from what it is in our first example—the division of a nerve.

In the recovery that occurs to a small extent when important conducting paths are cut across in the central nervous system, restoration is not due to the healing of the injured tracts, nor to the regeneration of the divided threads, which are called nerve-fibres; but to the happy circumstance that the complex labyrinth of conducting paths has so many cross connections that it is possible for impulses to avail themselves of these, and so reach their destination by a new channel. There is absolutely no recovery if the division of the spinal cord is complete, for then all possible channels are equally blocked.

In a nerve, recovery will occur if the division is absolute, and in this case restoration of function is due to the regeneration of the nerve fibres. It is the object of this paper to describe the manner in which this regeneration occurs.

Nearly every one has suffered at some time from minor injuries in the way of skin wounds, and has doubtless for a time experienced anæsthesia or loss of sensation on one side or other of the cut. Some months later sensation returns, and the accident is forgotten. Regeneration of the nerves necessary for this usually occurs without any surgical aid, and and all that remains is a scar. Scar tissue, or cicatricial tissue, as it is technically termed, is a dense kind of connective tissue somewhat stronger and firmer than the ordinary skin. This same kind of tissue is formed in the repair of all injured structures in the body. When, for instance, a muscle or a tendon is cut across, the formation of cicatricial tissue to bridge across the gap is quite sufficient to restore the continuity and uses of the injured organ. If a rope is divided, it does not matter what sort of material—silk, hemp, or cotton—is used to tie the ends together; if the repairing material is sufficiently strong the rope is as good as ever. So it is with the haulage mechanism of the body: a tendon or a muscle can pull upon the bones quite as well as before the accident, even although the repairing tissue is not identical with that which was injured.

But the case of a nerve is different. If a telegraph wire is divided the repairing material must be wire, or at least something capable of conducting electricity. The molecular change transmitted along nerve fibres, and which is termed a nervous impulse, is so peculiarly the property of nerve fibres, that no amount of scar tissue is efficacious in restoring function. Nerve fibres must be mended by nerve fibres and by nothing else. Indeed, a large amount of cicatricial tissue is harmful, for its very density is an obstacle to the successful growth of the new fibres which ultimately penetrate it.

We must never push the telegraphic simile too far in dealing with the nervous system, useful as it is in talking of such matters to students. If a telegraph wire is broken, all that is necessary in healing the damage is to connect the ends with another piece of similar wire; the two segments of wire which are united are not injured throughout their length, and conduct the electrical impulse as well as ever. In the case of a nerve it is different; the stretch of nerve still united to the central nervous system is spoken of as the central end; this consists of long threads which are the outgrowths of protoplasmic masses, termed nerve cells, situated in the grey matter of the central nervous system. The central end of a divided nerve remains healthy, or approximately so. The other segment, which is called the peripheral end, consists of nerve fibres also, but after division they soon lose their power of responding to stimuli and of conducting nerve impulses. They simultaneously undergo a degenerative change, which can be easily recognised by the microscope, and ultimately atrophy. These fibres having been cut off from the nerve cells—of which they are outgrowths—are no longer capable of receiving that nutritive control which it is the special object of these protoplasmic masses to accomplish. This was first pointed out by the elder Waller, and the term "Wallerian degeneration," by which it is known, is a permanent record of this historical fact.

Even the most rapid suturing of the divided ends together is ineffective to prevent Wallerian degeneration from occurring in the distal segment.

This shows the difficulties attendant on the process of nerve regeneration; for the new fibres have not only to bridge a gap, but they are also necessary to replace the degenerated fibres in the peripheral segment right down to its ultimate and final ramifications in skin, muscles, or other organs.

In the elucidation of the problem as to how this is accomplished, experiments upon animals have been rendered necessary, so as to extend and complete the imperfect information, which is all that can be obtained by clinical observation in man.

But in order to pave the way to this, it is first necessary to allude to the way in which nerve fibres find their way to the periphery from the central nervous system in the embryo. The central nervous system (brain and spinal cord) is originally formed by an infolding from the surface of the most external embryonic layer known as the epiblast, the remainder of the epiblast appearing in the fully formed animal as the epidermis. This infolding is cut off from the surface epiblast, and an island tube of epiblast is converted by thickening of its walls into the brain in front and spinal cord behind. Its walls contain numerous masses of protoplasm, or primitive nerve cells, which are called neuroblasts. At first these cells have no processes, but branching projections grow out from each; these interlace with the similar processes of other cells, and so bring neighbouring cells, and even distant cells, into communication with each other, to ensure harmonious or co-ordinate action between them. But these branching processes or dendrons are not the only outgrowths of the nerve cell, nor are they the first to make their appearance. The first outgrowth to appear is stouter than those that follow; it grows to the greater distance; it leaves the central nervous system altogether, and ultimately penetrates to peripheral structures. It is known as the axon, and, with few exceptions, every cell body has only one axon. It ultimately becomes the axial conducting core of a nerve fibre, and a collection of these fibres constitutes the bundle known as a nerve. At first the axon is naked throughout its entire length, but later in development it becomes sheathed. The sheaths of the axon are certainly important for its nutrition, and possibly insulate the axon, much as a telegraph wire is insulated from its fellows by a silk or gutta-percha covering. In the fully formed nerve each fibre then consists of an axon or axis cylinder; outside of this is a thick white sheath, which contains complex phosphorised fats—this is known as the medullary sheath or white substance of Schwann; outside of this is a delicate nucleated membrane called the primitive sheath of Schwann, or more usually the neurilemma. Certain new fibres, however, never receive a fatty sheath, and are consequently called non-medullated; these are the fibres which supply the involuntary muscular fibres of the internal organs of the body.

This view, that each nerve fibre develops as an independent outgrowth from a nerve cell, and grows distalwards, finally becoming united to other tissues (*e.g.* muscle fibres) in the periphery of the body, is associated especially with the name of His, and has been accepted by the majority of embryologists.

There have been other views held, but it will be sufficient here to mention only one of these; for it is the one which, next to that of His, has been favoured by investigators. Briefly it is as follows: The nerve fibre is not a secondarily formed bridge between the central nervous system and the peripheral organs, but exists from the very first, and in subsequent development it merely undergoes elaboration, and increases in bulk and in length as the distance from the central nervous system and the periphery increases with the increasing size of the developing animal.

I shall not fully discuss the pros and cons of this controversy, but only say that the available evidence appears to me strongly in favour of the first of the two views, and it has within the last few months been supported by a very remarkable ocular demonstration of its truth. Mr. Ross Harrison has, in the Johns Hopkins University, Baltimore, actually seen the fibres growing outwards in embryonic structures. Pieces of the primitive nervous tube which forms the central nervous system were removed from frog embryos, and kept alive in a drop of lymph for a considerable time; the cilia of the neighbouring epidermic cells remained active for a week or more; embryonic mesoblastic cells in the vicinity were seen to become transformed into striated muscular fibres, and there was therefore no doubt that even under artificial conditions of this kind—rendered necessary for microscopic purposes—life and growth were continuing. From the primitive nervous tissue, and from this alone, nerve fibres were observed growing and extending into the surrounding parts. Each fibre shows faint fibrillation, but its most remarkable feature is its enlarged end, which exhibits a continual change of form. This amœboid movement is very active, and it results in drawing out and lengthening the fibre to which it is attached, and the length of the fibre increases at the rate of about one micro-millimetre in one or two minutes.

I think these observations show beyond question that the nerve fibre develops by the overflowing of protoplasm from the central cells, and thus give us direct evidence in favour of the view which most embryologists previously held mainly as the result of circumstantial evidence. Such, then, being the general state of our knowledge regarding the way in which nerve fibres grow in the developing animal, it is not surprising to find that the prevalent idea regarding their regeneration after injury follows the same lines. The original teaching of the elder Waller (1852) that regeneration occurs by fibres growing out from the central stump into the peripheral segment of the nerve was formulated at a time when the relationship of nerve fibres to nerve cells was not so fully recognised as it is at present; and the Wallerian doctrine may be accepted with confidence to-day. It has, however, been questioned from time to time, and the earliest to hold an opposite view was Vulpian. Vulpian, working with Philippeaux, cut nerves in young animals, excising long portions so as to prevent the two ends uniting. Some months later they were surprised to find that new perfectly formed nerve fibres had appeared in the peripheral segment, and that this segment possessed the physiological properties of being excitable and capable of conducting nerve impulses. To this phenomenon they gave the name of "autogenetic regeneration." The publication of these results provoked a long controversy, which lasted from 1859 to 1874, and was closed at the latter date by Vulpian withdrawing his new idea. He did so because in the meanwhile he had repeated his experiments more carefully, and so discovered that, although the ends of the divided nerve had not joined up, connection with the central nervous system had nevertheless been re-established by means of fibres growing into the peripheral segment from other nerves cut through in skin and muscle in the course of the operation.

The controversy has been revived within the last few years, and the position of the disputants has been almost exactly the same as that occupied by Waller and Vulpian half a century ago. Modern investigators have, however, the advantage of being able to apply new methods of research, and are provided with many histological reagents of which the older workers were destitute. It is, however, never safe to argue entirely from microscopic appearances, for nerve fibres may be simulated by non-nervous structures, and a strand that looks like a nerve fibre is not really such unless it can be experimentally shown to be both excitable and capable of conducting nerve impulses.

Vulpian's old doctrine of auto-regeneration has been revived in this country by Ballance and Purves Stewart, and in Scotland by Kennedy. The most prominent and persistent supporter of the autogenetic theory is, however, a German neurologist named Bethe. But none of these investigators have excluded the fallacy which underlay the work of Vulpian and Philippeaux, as has been recently pointed out by Langley and Anderson. These two workers at first thought they also had obtained evidence of purely peripheral regeneration, and it was not until they carried out careful dissections that they convinced themselves that union with the central nervous system had occurred. The new nerve fibres which grow into the peripheral segment from other nerves divided in the operation, often do so by a devious and contorted course. If the number of medullated nerve fibres in the peripheral end is small, then the connection with central fibres was found to be slight; and in cases where no connection occurred then medullated nerve fibres were entirely absent. Bethe admits a variability in the number of medullated fibres, and this, though easily explicable on the view that such fibres come by accident from the central ends of divided nerves, is not accounted for at all by the autogenetic theory.

Another admission which Bethe makes also weakens his view. He admits that auto-regeneration does not occur in adult animals. He does not, however, state at what age animals lose their power of auto-regeneration, nor explain how it is that after a certain date an animal repairs a divided nerve in the exactly contrary manner to that it would have adopted if the nerve had been cut before that date. The difference which exists between young and adult animals is quite easily accounted for in accordance with Wallerian views; it is simply due to the greater ease with which reunion with central nerves occurs in young and actively growing animals.

Bethe's views have been contested not only by Langley and Anderson, but also by Lugaro, by Kölliker, by Cajal, by Marinesco, by Mott, and Edmunds in conjunction with myself, and by numerous others.

I may mention a few of the experimental results which have come out of the renewed work elicited by the promulgation of the autogenetic theory.

(1) It is possible entirely to prevent reunion with the central ends of divided nerves. In our own work we accomplished this by removing a long stretch of the main nerve experimented with, by making the skin incision as small as possible, and by inclosing the top end of the peripheral segment in a cap of sterilised gutta-percha. Under such circumstances no auto-regeneration occurs.

(2) Pieces of nerve may be transplanted under the skin, and in time a few fully formed medullated fibres appear within the degenerated bundle of fibres. This is adduced by Kennedy as undoubted evidence of auto-genesis, but, again, is easily

explicable on the hypothesis that the new fibres had wandered in from cutaneous nerves divided in the course of the operation, and we showed that if this fallacy is excluded by transplanting the nerve, not into the subcutaneous tissues, but on to the stomach wall in a sheath of peritoneum, no regeneration occurs at all.

(3) The late appearance of the medullary sheath in those portions of the regenerating fibres which are most distant from the place where the nerve is originally cut and sutured, is a conclusive piece of evidence that the new nerve fibres grew from the central end in a peripheral direction.

(4) After regeneration has occurred, the nerve may be again cut across, either on the central side of the original point of section (as in Langley and Anderson's work), or on the peripheral side of the original seat of operation (as in our own work). In the former case Wallerian degeneration occurs in all the new fibres, showing that they were all under the nutritive control of the cells of the central nervous system. In the latter case the degeneration took place solely on the peripheral side of the second cut. The direction of degeneration is always the direction of growth, so this experiment shows that the growth of the new fibres had not started from the periphery centralwards, but in the reverse direction. On looking up the literature of the subject, I found that Vulpian also did this experiment with the same result, and it can hardly be doubted that this formed one of the factors that later led him to abandon the autogenetic theory. An experiment on somewhat the same lines has been carried out recently by Lugaro: he has shown that regeneration of the cut nerves connected with the lower part of the spinal cord does not occur after that part of the spinal cord has been extirpated. This is a very striking piece of evidence, showing the dependence of the growth of fibres on the activity of the cells of the central nervous system with which they are originally connected. Ocular evidence is, however, perhaps more convincing than the description of experimental results, so I will next present to the readers of SCIENCE PROGRESS drawings of some of the microscopic specimens prepared by the latest improved methods.

Cajal, by the help of his new silver method, comes to the conclusion that the new formation of nerve axons in the peripheral stump is exclusively due to growth from the central end.

He figures the long and often contorted course of these growing fibres in the swelling at the cut central end, and shows that they ultimately reach their goal—the peripheral segment—in time and in spite of all hindrances. The greater the obstacles interposed the later does the union and consequent regeneration in the peripheral end occur. He also draws attention to the

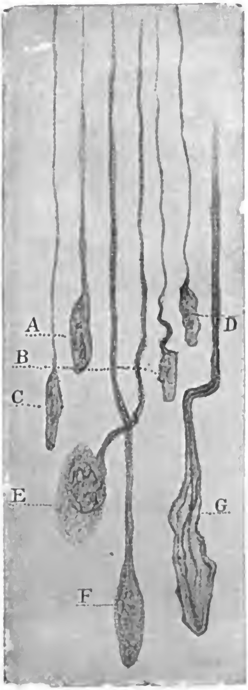

Fig. 1.—Olive-shaped swellings at the ends of nerve fibres growing distalwards from the central ends twenty-one days after the nerve had been divided. (Marinesco.)

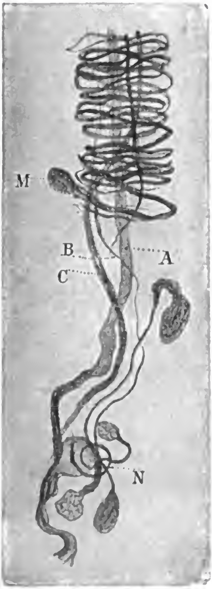

Fig. 2.- Spiral forms often seen in regenerating nerve fibres: the fibres are seen to be of varying thickness, and each is provided with a terminal swelling. (Marinesco.)

olive-shaped swelling at the free end of each growing axis-cylinder. These are also figured by Marinesco, and I am indebted to the kindness of Prof. Marinesco for figures 1 and 2, which illustrate these swellings; in figure 2 the convoluted course of the new fibres, which is so frequently seen, is shown.

Marinesco calls attention also to the fact that these terminal swellings, although they may roughly be described as olive-shaped, vary a good deal in external form; this is shown in the drawings, and is quite intelligible now that we have Ross Harrison's description of the constant changes of form they exhibit in embryonic history. In regenerating fibres we have not direct evidence that similar amœboid movements take place, for the preparations were made not while the fibres possessed vitality but after fixation with a suitable hardening reagent. Still, the mere fact that they are fixed in various shapes is conclusive evidence that they do exhibit these changing outlines.

Marinesco has passed through the stage so often seen in those who have attacked the problem of nerve repair. In his earlier publications he thought his preparations afforded evidence of auto-regeneration, though he never went as far as Bethe has done in that direction. In his latest papers he has entirely recanted these views, and is now convinced that auto-regeneration is a myth. I reproduce two more of his very beautiful illustrations. The preparations were stained by Cajal's new method, and they require but little comment.

They show the new fibres penetrating the cicatricial tissue of the junction from the central end in a peripheral direction; they show the absence of any new axons developed autogenetically in the peripheral end. Such preparations ought to carry conviction to those who have any lingering belief in auto-regeneration, that the Wallerian view is the only possible one to adopt.

It must not, however, be supposed that the peripheral end is entirely inactive; for while degeneration is progressing in the axons and their fatty sheath, an active multiplication of the cells of the primitive sheath or neurilemma is taking place. These neurilemmal cells probably play a nutritive action towards the more important structures within them, and Graham Kerr, in a recent study of nerve growth in the fish *Lepidosiren*,

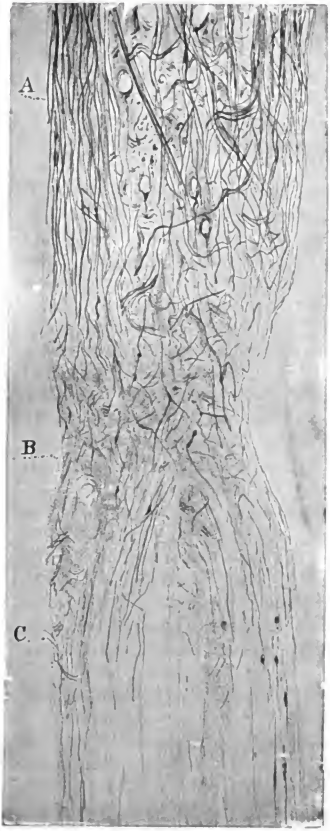

Fig. 3.—Longitudinal section of sciatic nerve of new-born dog eight days after the nerve had been divided. Union had already taken place. At the extremity of the central end (A) growing fibres are seen running in various directions towards the cicatrix (B); C is the peripheral end, into which a few fibres are already penetrating. (Marinesco.)

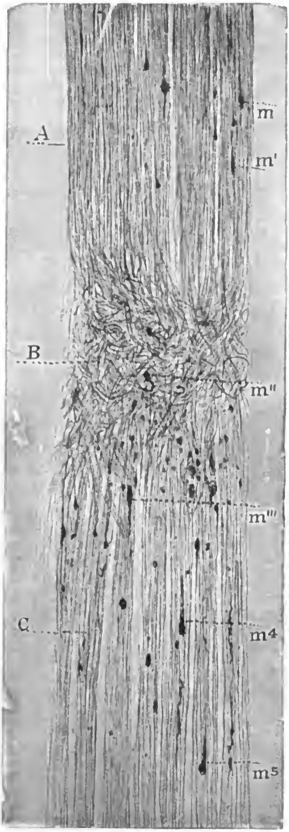

Fig. 4.—Longitudinal section of dog's nerve, twenty-one days after the nerve had been divided. A more advanced condition is seen than that shown in fig. 3. A is the central end; B the cicatrix of union, where the nerve fibres are seen in great numbers taking an irregular course. Into C, the peripheral end, many fibres have already successfully penetrated; m, m′, m″, etc., are the terminal swellings of fibres growing from the central stump and directed towards the periphery, except in the case of m″, where the twisting of the new fibre in its efforts to grow had, at the time when the animal was killed, directed the termination backwards. (Marinesco.)

has supported in a very conclusive and entirely independent way the view that Mott and I advanced some years ago of the value of the neurilemma in maintaining the nutrition of the axis cylinder. There is but little doubt also that these cells act as phagocytes in the removal of the degenerated products of the other portions of the nerve fibre. But after this is accomplished they elongate and unite into long chains. It is this appearance that has led some observers into regarding them as true nerve fibres; they have jumped to the conclusion that the neurilemmal cells are also able to form a conducting core, and so have regarded auto-regeneration as a histological possibility. But all recent observations by the best methods, as I have already stated, have failed to discover either an axial core or a fatty sheath in these "embryonic fibres" as they have been termed. Howell and Huber put it very well nearly twenty years ago when they said the peripheral structures are able to prepare the scaffolding, but the axon, the essential conducting core of the fibre, has an exclusively central origin.

The change in the neurilemmal cells which occurs in the peripheral segment is even more vigorous at the central termination of the cut nerve; here its nutritive function (or apotrophic function, as Marinesco calls it) is effective, and provides for the nourishment of the actively lengthening axis cylinders. At the peripheral end, unless the axons reach it, it is ineffective in so far as any real new formation of nerve fibres is concerned. If, however, the axons reach the peripheral segment, the work of the neurilemmal cells has not been useless, for they provide the supporting and nutritive elements necessary for their continued and successful growth. Moreover, the neurilemmal activity appears to be essential. In the white fibres of the central nervous system the neurilemma is absent; in this situation not only is the removal of the products of degeneration a very slow process, but, as I have previously mentioned, regeneration does not occur.

Having now considered the manner in which nerve regeneration occurs as elucidated by experiments upon animals, we can next pass to a study of the problem in man. When the accident is a slight one, or when a surgeon during an operation necessarily divides a number of small cutaneous and similar nerves, the process of repair may be confidently left to nature. But when a large nerve trunk is divided, the case is a different one—for a large nerve on division curls up at the end, forming a contorted leash of fibres; it also retracts, and a considerable amount of scar tissue is formed. This cicatricial tissue, by the time the nerve has begun to regenerate, has become very dense, and so an impediment to the successful growth of the nerve fibres is interposed. Still, in spite of such a barrier, spontaneous restoration frequently takes place. If the cut were made by a dirty piece of sharp machinery, inflammation usually comes in as a complication, and causes still further delay. In animals, where the cut is made with a clean knife, and antiseptic precautions are employed, this danger is reduced to a minimum, the amount of scar tissue is less, and union may be anticipated without suture. But even here suture hastens recovery, and in man thorough cleansing of the wound and the union of the divided nerve by appropriate ligatures should always be carried out. The growing nerve fibres will then not be left to themselves to find their way into the peripheral end, but will be guided more rapidly to their destination. In a number of cases where the carelessness of the patient has caused him to neglect obtaining this surgical assistance, it may be years before restoration of function takes place, but even under these circumstances the surgeon can help him. The old wound is opened up, the swollen lumps at the ends of the two segments of nerve are removed, and the two ends can then be united; the operation is spoken of as "secondary suture," and recovery is then comparatively rapid.

In some cases where the gap is a long one, some surgeons have been in the habit of transplanting a piece of nerve obtained in a living condition from a recently killed animal to bridge across the interval. This, however, is not to be recommended, since Marinesco has shown that if a transplanted nerve is obtained from another species of animal it is completely necrosed, just as the blood corpuscles of one animal are destroyed by the body fluids of another. The interposition of a foreign piece of nerve is thus in man rather a hindrance than a help.

Many surgeons have been steadfast upholders of the autogenetic theory because they have found in man that sensation may return very rapidly after freshening up and suturing together the ends of a nerve which had been divided a long time previously. They argue that during this time new nerve fibres must have been produced in the peripheral segment, which would be ready to exercise their functions directly they are placed in continuity with the fibres of the central end.

Examination of these cases shows, however, that sometimes the conclusion has been a hasty one, depending largely on the evidence of the patients themselves, in whom the wish is father to the thought. There was a case of this kind recently in King's College Hospital. Very shortly after the operation the patient stated he was able to feel, but these sensations rapidly subsided, and sensation did not really return until months later. The preliminary sensations were doubtless subjective; the irritation of the nerve in the scar lasted some hours, and the sensations so produced were referred by the patient's mind to the original terminals of the fibres.

In other cases the genuineness of the early recovery is doubtful, because insufficient care is taken in testing the patient's sensations. In spite of sensitiveness to such tests as needle pricks, there is usually absolute anæsthesia to the far more delicate test of stroking the hairs over the affected region until quite late dates. Head and Sherren have recorded a large number of surgical cases, but evidence of early recovery is usually lacking; there is some difficulty in localising the stimulus so that it should not affect the hyperæsthetic marginal zone of the anæsthetic region, and if this danger is recognised it can be avoided. Another pitfall is this: the deep sensibility of the subjacent parts, such as would be excited by needle pricks, or by pressure, is entirely independent of cutaneous sensation. The fibres subserving this form of sensation run mainly with the motor nerves, and are not destroyed by division of all the nerves to the skin. Neglect to recognise this fact will explain some of the results of those who have published cases of early recovery.

The difficulty of clinical observation on others induced Dr. Head to combine with his experiments on animals and his observations on patients, an experiment on one of the sensory nerves of his own arm. This gave an opportunity for the study of the phenomena by a trained observer upon himself. He certainly experienced no early return of function, and the date at which sensation did come back coincides closely with the dates obtained in animals by physiologists for the reappearance of new and fully formed nerve fibres.

In the course of this work he made the interesting discovery that the first kind of sensation to return is of a vague nature, which he terms *protopathic*; he associates this with the activity of the fine medullated fibres which replace the degenerated ones at an early date; return of protopathic sensibility begins about the eightieth day. The more elaborate sensations and power to localise them accurately return much later, and this *epicritic sensibility*, as Head terms it, is usually not perfect until months, or even years, have elapsed after the regeneration started.

By this time, as was shown by experiments on animals, the fine nerve fibres which subserve protopathic sensation are largely admixed with a later growth of larger nerve fibres, and he believes that epicritic sensation is subserved by these. He also postulates that the three kinds of sensation (deep, protopathic, and epicritic) are related to different kinds of end-organs in the peripheral structures.

Granting that earlier observers had been led into errors by not being acquainted with Head's discoveries, and that many cases of supposed early recovery can be explained in the manner already indicated, there remains a small residuum of cases in which such explanations do not hold, and in which early recovery appears to have been an undoubted fact. Of these, I would particularly refer to some cases recorded by Dr. Kennedy of Glasgow, in which the return of sensation of some sort, especially to painful stimuli, was a matter of only a few days. In these cases due care appears to have been taken to exclude any bias of the patient's own mind. He admits that such cases are rare; from his own point of view auto-regeneration would therefore appear to be an unusual phenomenon. Granting that the early recovery was genuine, it seems to me there is a much more probable explanation than that of auto-regeneration. They are doubtless instances where extremely rapid growth of new axis cylinders from the central into the peripheral segment of the nerve took place. Dr. Kennedy's cases appear to be happy examples of the date of the secondary suture being such that the usual impediments to repair were minimal. The preparatory work of the neurilemmal cells in the distal portion of the nerve had evidently reached that stage when they were most fitted to receive the new axis cylinders, and by their metabolic activity favour the onward growth of the fibrils at a rapid rate. The examination of

Dr. Kennedy's own records supports the same view. In three of his four cases sensation returned first in the parts nearest the suture, and later in more distant parts, such as the finger tips. This surely proves that regeneration was occurring in a peripheral direction. The record of the fourth case gives no details of the order of recovery. The only difficulty remaining is the unusual rapidity of the reparative process. I say "unusual" because most of our ideas of the rate at which axis cylinders grow are derived from cases in which gross impediments to growth are present. I have, however, been struck in some of our own observations with the rapidity with which the central unites with the peripheral end, even when an inch or more of nerve has been excised. In some cases there was a well-defined strand of union after a few days. This is especially the case when young and vigorous animals are employed. In two of Dr. Kennedy's cases, the patients were in the prime of life (aged twenty-nine and thirty-seven respectively); the other two were children—aged six and sixteen respectively.

The introduction of the new methods of Cajal has now furnished us with a method of tracking the growing axis cylinders with a certainty which was previously lacking; and Marinesco, availing himself of these methods, has shown that the lengthening of the regenerating fibres is demonstrable twenty-four hours after a nerve has been cut.

This concludes what I have to say on an important problem of what we may call applied physiology. In the present state of our knowledge it is impossible to avoid controversial questions. The proverbial disagreement between doctors is specially true of physiologists, and really this is only as it ought to be. Whilst knowledge is in the making there must be divergencies of opinion, and it is only by a full and free discussion of these, and by the renewed research of which criticism is the stimulus, that any certainty in the way of truth can be arrived at.

MENDELISM

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Perhaps the most interesting, certainly the most sensational, chapter in the history of biology, when it comes to be written, will be that which deals with the discovery of Mendel's papers and with the fruit which that discovery has borne. We are already in possession of all the material for the former topic; and the first instalment of the fruit which has already been harvested augurs well for the quality of what is to come.

In 1865, a man absolutely unknown to the biological world, Gregor Johann Mendel, read before a meeting of the Natural History Society of Brünn a paper on his experiments with Peas, entitled "Experiments with Plant Hybrids." To-day no name is better known to biologists than that of Mendel. And yet, when he died in 1884, he was as obscure as when he read his famous paper. Indeed, it was not until sixteen years after his death that Mendel suddenly burst from obscurity into fame.

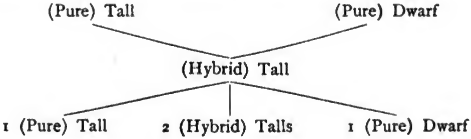
In 1900 Mendel's experiments with Peas were repeated, and his results confirmed, independently by De Vries in Amsterdam, Correns in Leipzig, and Tschermak in Vienna. This spark—the discovery of Mendel's paper—has been responsible for the generation of an enormous amount of energy, which has manifested itself ever since in a continually smouldering train of investigation; and on one or two occasions in explosions of controversial violence.

We must now make it our business to become familiar with the facts which Mendel discovered, and with the interpretation which he put upon them. Mendel found that varieties of the culinary pea, *Pisum sativum*, could be classified according to a number of constant, true-breeding characteristics, such as the form of the plant, whether normal (*i.e.* tall) or dwarf; or such as the colour of the cotyledons of the seeds, whether yellow or green; and so forth.

Mendel crossed a Tall with a Dwarf. The resulting hybrid was invariably a Tall. Tallness, therefore, he called the *dominant* character and dwarfness the *recessive*.

These hybrids were allowed to self-fertilise (the normal process in *Pisum*), and seeds gathered from them gave, when grown, 1064 plants, of which 787 were tall and 277 dwarf; that is to say, the hybrid Talls produced Talls and Dwarfs in the proportion of 2·84 to 1, or roughly 3 to 1.

The seeds of these plants were sown, and it was found that all the Dwarfs bred true, whilst of every three Talls, one produced only Talls, the other two giving rise to Talls and Dwarfs in the proportion 3 to 1. The foregoing account may be summarised in the following diagram:



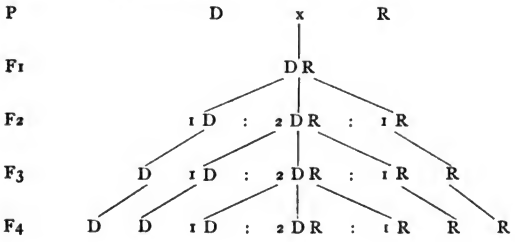
Let us now look at the three kinds of Peas which compose the generation in which Pure Talls, Hybrid Talls, and Pure Dwarfs appear in the proportion 1 : 2 : 1. We already know that all the Dwarfs breed true, that a third of the Talls breed true, whilst the rest of the Talls produce Talls and Dwarfs in the proportion 3 to 1. This proportion—3 to 1—is made up in the same way as the same proportion in the preceding generation—namely, 1 Pure Tall; 2 Hybrid Talls; and 1 Pure Dwarf. All these Dwarfs breed true; all the Pure Talls breed true; and the Hybrid Talls produce Talls and Dwarfs in the proportion 3 to 1. And so on.

There are two sets of symbols which are very convenient in describing these phenomena.

The first set describes the different kinds of individuals; the second the generations. D denotes the dominant form (in the case we have been discussing, the Tall), R the recessive (the Dwarf), and D R the hybrid.

P denotes the parental generation; F1, the result of crossing the two parent forms—in our case, the Hybrid Tall; F2 denotes the next generation, *i.e.* that in which the dwarfs reappear in the proportion 25 per cent.

We may now summarise the Mendelian phenomenon in the following diagram:



What is the cause of this beautifully regular and definite phenomenon? Mendel answered the question in this ingenious way. He believed that the germ-cell of the hybrid pea did not represent a mixture of tallness and dwarfness, but that a germ-cell represented *either* a tall *or* a dwarf, and, moreover, that half of the germ-cells represented tall and half of them dwarfs. Let us see what is the result of the union of—say—a hundred male germ-cells, or pollen-cells, with a hundred female germ-cells, or egg-cells. Before we proceed, let us make certain of two points which are essential to the argument. Mendel believed that a pure-breeding tall pea contained only tall-representing germ-cells—in fact, that the reason that it bred true was that it did contain them; and that the dwarf contained only dwarf-representing germ-cells. Mendel had also found that the result of a union between a "tall" germ-cell and a "dwarf" one was a hybrid which bore the tall character. Now let us return to our argument.

Fifty of the hundred pollen-cells would be "tall," and fifty "dwarf." Let us consider the "talls" first. As half of the eggs-cells are "tall" and half "dwarf," the "tall" pollen-cell has an equal chance of meeting a "tall" and a "dwarf" egg-cell. So that twenty-five of the "tall" pollen-cells would meet "tall" egg-cells, and twenty-five would meet "dwarf" ones; and the resulting unions would be (writing T for Tall, and D for Dwarf):

25 T T
25 T D

Similarly twenty-five of the fifty "dwarf" egg-cells would meet "talls" and twenty-five "dwarfs," or briefly:

25 D T
25 D D

The total result therefore is:

25 T T
25 T D
25 D T
25 D D

Now we already know that the result of the union of a "tall" with a "dwarf" germ-cell is a hybrid which is tall, and Mendel found that it made no difference whether the tall character was carried by the male parent and the dwarf by the female, or *vice versa*. So that the above result can be written:

25 T T (Pure Talls)
50 T D (or D T) (Hybrid Talls)
25 D D (Pure Dwarfs)

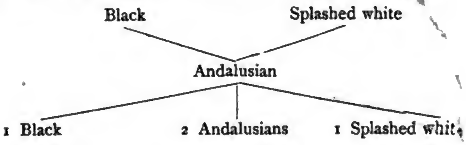
The result of the random union of two sets of germ-cells, each set consisting of 50 per cent. of germ-cells bearing the Recessive and of 50 per cent. bearing the Dominant character, can be admirably illustrated by drawing one counter at random from a hat containing fifty Red and fifty White counters, and another from another hat with similar contents, and by placing the three kinds of pairs in three separate rows on the table, according as whether they are R W, R R, or W W. The larger the number of trials you make the closer will the approximation to the proportion of 25 R R, 50 R W, 25 W W be. Counters are worse than marbles for illustrating this, by reason of the difficulty of thoroughly shuffling them. But they are better than them, because the phenomenon of dominance and the proportion 3 : 1 can be illustrated with them, the former by merely making it a rule to put the red counter on the top of the white when a red and a white are drawn together, the latter by superposing the upper counter in every pair so carefully that the lower one is invisible. If this is done effectively there will be seen, at any rate from a slight distance, to be 75 per cent. red counters and 25 per cent. white. But if you jog the table the difference between the previously apparently identical reds will be revealed. It is also very easy to illustrate subsequent results with the counters. The result of mating the hybrids in F2 can be illustrated in exactly the same way as that of mating the F1 hybrids. And it is readily seen that it is no more possible to get anything but Dwarfs from the Dwarfs in F2 than it is possible to get anything but pairs of white counters by drawing from two hats each containing nothing but white ones, and that it is no more possible to get anything but Talls from those Talls, *i.e.* the pure ones, which resulted from the union of like gametes than to get anything but pairs of reds from drawings from two hats containing only reds.

The animal or plant resulting from the union of two germ-cells or gametes—and all animals and plants which reproduce sexually result from such a union—is called a *zygote*; that resulting from the union of like gametes or germ-cells is called a *homozygote*; that from the union of unlike gametes a *heterozygote*.

The heterozygote in the case which we have been considering as an example was only distinguishable from the dominant homozygote by the fact that when allowed to self-fertilise it produced Dwarfs as well as Talls. But sometimes the result of crossing two pure strains is different from either of them—that is to say, the heterozygote has a character peculiar to itself. This makes it possible to distinguish between the heterozygotes and the dominant homozygotes in F2 otherwise than by breeding from them.

The phenomenon may be illustrated by the famous case of the Andalusian fowl. If you buy a pair of these birds from the very best source you will find that they will not breed true, but that they will produce besides the Andalusians blacks and splashed whites, and that on the average these three forms will be produced in the proportion 1 black, 2 Andalusians, 1 splashed white. If you were not acquainted with Mendelian phenomena, but were guided by the principles of heredity which were universally held in pre-Mendelian days (and are still by those who are not Mendelians), you would sell the blacks and whites for eating and breed from the Andalusians, in the belief that, as they at least, to your own personal knowledge, had an Andalusian father and mother, they would be more likely to breed true than a pair of Andalusians of unknown and, as you would expect from the result of mating them, of mixed parentage. Your anticipation would not be fulfilled. Your Andalusians would again produce blacks, Andalusians, and splashed whites in the proportion 1 : 2 : 1. But if you were acquainted with Mendelian phenomena you would immediately suspect that the Andalusian was a heterozygote form, and that the two homozygote forms which by their union gave rise to it were the blacks and the splashed whites. This is indeed the case. Mate the black with the splashed white, and you get nothing but Andalusians. The obvious plan, therefore, instead of selling the blacks and whites to the poulterer and keeping the Andalusians to breed from, and then only getting 50 per cent. of what you want, is to sell the Andalusians to fanciers, keep the blacks and whites, and get 100 per cent. of Andalusians by crossing them, making occasional matings of Andalusians to keep up the supply of blacks and whites.

This case is summarised in the following diagram:



Let us now return to the Peas. We have referred in detail to only one pair of characters, namely, Tall and Dwarf. Mendel dealt with six other pairs of characters, namely:

1. The shape of the ripe seeds, which was either round or wrinkled.
2. The colour of the ripe cotyledons in the seed, which were either yellow or green.
3. The colour of the seed-coat, which was either white or grey (with or without purple spots).
4. The texture of the ripe pods, which was either hard and inflated or soft and constricted between the seeds.
5. The colour of the unripe pods, which was either green or yellow.
6. The arrangement of the flowers on the stem. The flowers either came off normally at the nodes along the stem, or they were situate in a bunch at the top of the stem; this latter is the so-called Mummy habit.

The two members of each of these pairs of character stand to one another in the relation of dominant and recessive. In the above list the dominant member of each pair is written first. The two characters which form such a pair are called *allelomorphs*; and green is said to be allelomorphic to—*i.e.* forms the other member of a pair with—yellow. Similarly yellow is allelomorphic to green.

We have so far, in considering the results of crossing an animal or a plant, paid attention only to a single pair of allelomorphs, tall and dwarf, black and splashed white. We must now ask ourselves, What is the relation between character belonging to different allelomorphic pairs? And the answer, broadly speaking, is that in the case of some characters there is no relation, whilst in the case of others there is; or, to amplify the answer, in the case of some characters the members of distinct allelomorphic pairs exercise a very definite effect on one another, whilst in the case of others they are entirely independent of one another. We will deal with the latter case first, because it is simpler.

What the result of mating a green round with a yellow wrinkled pea will be, can be answered by reference to the table of characteristics on p. 434, in which (it will be remembered) the dominant member of a pair is written first. The result will be a yellow round one. What the result of allowing these to self-fertilise will be can be predicted from the result of making drawings of two counters from each of two hats, which contain equal numbers of green and yellow, red and white counters.

The number and nature of the possible combinations is given by the number and contents of the squares in the Table on p. 436.

Y and G stand both for yellow and green counters and "yellow" and "green" germ-cells; R and W stand both for red and white counters and "round" and "wrinkled" germ-cells. The four pairs of letters along the top of the table represent the four kinds of male gametes; the pairs along the side the four kinds of female ones; the squares represent zygotes. Let us consider the results of their union, beginning at the top left-hand square. (In the following account Y is to be read as yellow, G as green, R as round, and W as wrinkled.) Here we have to do with union between two Y R gametes. The result is a pure Y R zygote. In the square to the right of it, it is a case of a union between a Y R egg-cell and a Y W pollen-cell; the result is a Y R zygote, which is a homozygote regards colour and a heterozygote as regards shape. In the next square to the right a Y R gamete meets a G R gamete; the result is again a Y R zygote, which differs from the last in that it is homozygote as regards shape and heterozygote as regards colour. In the last square on the top line a Y R gamete meets a G W one; the result is a Y R which differs from any of the preceding ones by being heterozygote both as regards colour and shape. And so on throughout the table. The nature of the sixteen possible kinds of unions of gametes is written in small letters in the sixteen squares of the table. The characters of the resulting zygotes are written in large letters. When this explanation is being illustrated with counters, the nature of the zygote in each case is given by making it a rule always to put a yellow on the top of a green counter and a red on the top of a white.

	YR	YW	GR	GW
YR	YR × YR. 1. YR	YR × YW. 2. YR	YR × GR. 3. YR	YR × GW. 4. YR
YW	YW × YR. 5. YR	YW × YW. 6. YW	YW × GR. 7. YR	YW × GW 8. YW
GR	GR × YR 9. YR	GR × YW 10. YR	GR × GR 11. GR	GR × GW 12. GR
GW	GW × YR 13. YR	GW × YW 14. YW	GW × GR 15. GR	GW × GW 16. GW

The result therefore of allowing our Y R hybrid (produced by Y W and G R) to self-fertilise should be:

9 Yellow round (squares 1, 2, 3, 4, 5, 7, 9, 10, and 13).
3 Yellow wrinkled (squares 6, 8, and 14).

3 Green round (squares 11, 12, and 15).
5 Green wrinkled (square 16).

Or, briefly, 9 Y R, 3 Y W, 3 G R, 1 G W in every sixteen peas.

Of the 9 Y R, only 1 (square 1) is homozygous in both respects, and should produce only Y Rs. Two Y Rs are homozygous in colour only, but heterozygous in shape (viz. squares 2 and 5); they should produce only yellow, but both "Rounds" and "Wrinkleds." Two Y Rs are homozygous in shape, but heterozygous in colour (viz. squares 3 and 9); they should produce only rounds, but both "Yellows" and "Greens." The remaining 4 (squares 4, 7, 10, and 13) are heterozygous both in colour and in shape, and should produce all 4 kinds—Y R, Y W, G R, and G W.

On the 3 Y W, 1 (square 6) is homozygous in both shape and colour, whilst the remaining 2 (squares 8 and 14) are homozygous in shape only. Similarly with the 3 G Rs, that in square 11 is homozygous in both respects, the other 2 (squares 12 and 15) being homozygous in colour only. It will, of course, be noted that the character in respect of which all the 3 Y Ws and all the 3 G Rs are homozygous is a recessive one—namely, wrinkledness in Y W and greenness in G R.

There is only 1 G W zygote which, since both its characters are recessive, is therefore homozygous in both respects.

A very close approximation to the result 9 Y R, 3 Y W, 3 G R, 1 G W has been obtained in experiments by Mendel, Bateson, Hurst, and myself. And the various types of Y R, Y W, and G R have also been recognised.

Another point of view from which the proportion 9:3:3:1 may be regarded is from that of the zygotes solely. If we have a generation which displays the two characters of one pair Y and G in the proportion 3 Y to 1 G in every 4, and the two characters of another pair R and W in the proportion 3 R to 1 W in every 4, and if we further suppose that the two pairs are independent of one another, we should expect that in every 16 (= 4 × 4), 9 (= 3 × 3) would be Y and R, 3 (= 3 × 1) Y and W, 3 (= 3 × 1) G and R, and 1 (= 1 × 1) G and W. And we find that this is so, which shows that the two pairs are independent of one another.

Having become familiar with the signification of the 9:3:3:1 proportion, let us proceed to the discussion of other results which can only be interpreted in the light of it. We need not leave the Pea for illustration. If we ask a corn-dealer for a pennyworth of Maple or Partridge Peas, he will give us a kind of pea the seed-coat of which at first glance appears a uniform brown, but on closer inspection is seen to have a ground-colour of a pale brown, on which is a very beautiful mottling, consisting of anastomosing tracts of a rich brown colour. This type of coloration is called mapling. Another type of coloration is that which is often seen on (though it is not necessarily associated with) the kind of pea which is much grown and eaten on the Continent, and is known as the Sugar Pea. In this type of coloration there are minute spots (discernible by the naked eye) of slightly varying sizes and of a rich purple colour on a greenish grey background. The former type will be referred to as "maple" and the latter as "purple spot."

When a pea with a maple seed-coat is crossed with one with a purple spotted coat, the result is a pea on whose seed-coat both mapling and purple spots exist. This suggests that maple and purple-spot are not allelomorphic to one another, but belong to separate pairs which are supposed to be maple (M) and not-maple (nM), and purple spot (P) and not-purple spot (nP). This sounds very much like a logical exercise, a matter of words and not of things. But the reality of it is shown by breeding from the hybrids; for by doing this we actually get peas, which we can touch and see, which exhibit neither mapling nor purple spotting. We get, in fact, the following four types of peas in the proportions given by the numbers which precede them:

9 M P, 3 M, 3 P, 1 grey.

If we write this in a form analogous to—

9 Y R, 3 Y W, 3 G R, G W—

we should have:

9 M P, 3 M nP, 3 P nM, 1 nP nM.

The nP nM is grey because all these colours are on a background of pale grey. This proportion shows that we are dealing with two independent pairs of characters, viz.:

1. Maple and not-maple.
2. Purple spot and not-purple spot.

Now we come to those cases in which one of the characters of a pair of allelomorphs is not independent of a character in another pair.

We will cross a pea with a pale grey seed-coat, such as that which formed the background for the purple and the maple (many field peas exhibit no more than this grey colour), with a pea with no colour at all in its seed-coat, as is the case in a great number of the peas grown for the table. The result is a grey-seeded pea *on which there are purple spots*, which existed in neither parent. Heretofore this would have been labelled as an example of reversion and the matter would have been regarded as settled, or at any rate done with. But to call a thing reversion does not make one any wiser about it. Mendelism has provided a reasonable explanation of reversion in this case. Let us see how. The result of breeding from these grey-coated purple-spotted hybrids provided the clue. There were produced 9 grey with purple spots, 3 grey, and 4 white.

What does this mean? The 9 : 3 : 3 : 1 proportion suggests an explanation. It is supposed that here, as in the case of the cross between the maple and the purple spot, we are dealing with two pairs of allelomorphs, namely, (1) grey (G), and not-grey (nG), and (2) purple spot (P) and not-purple spot (nP). The grey pea exhibits the dominant grey character (G) of that pair. The white pea possesses—and here we come to the case of the interdependence of characters in separate pairs—the dominant purple spotting (P) of that pair; *but the purple spotting is not exhibited because one of its properties is that it cannot be manifested unless associated with the grey coat.* Bearing this theory in mind, let us write the 9 : 3 : 3 : 1 scheme for the two pair of allelomorphs G and nG, P and nP. It will be:

9 G P, 3 G nP, 3 P nG, 1 nP nG.

But we see that in the 3 P nG the purple spot is there, but the grey coat is not. Therefore *ex hypothesi* it will not be manifested and these three seeds will appear white, which gives the proportion 9 grey with purple spots, 3 grey and 4 white.

The possession by the hybrid of a character which neither of its parents possesses is accounted for by supposing that that character (in this case purple spotting) depends for its manifestation on two factors (in this case P and G), one of which exists in one parent and the other in the other. This Mendelian hypothesis therefore enables us to account for the reversion and for the otherwise meaningless proportion 9 : 3 : 4; or perhaps we should not say more than that the facts are consistent with the truth of this theory.

We will now pass from the culinary to the sweet pea, and describe Bateson's beautiful experiment. One of the countless varieties of the sweet pea grown to-day, Emily Henderson, a pure white, is remarkable for the fact that, whereas the pollen grains of most other varieties are cylindrical with almost parallel sides, some plants of it have this ordinary "long" pollen whilst others have *irregularly round pollen*. The irregularity is never so much pronounced that the round pollen can for a moment be mistaken for the long. It may help those familiar with peas and beans to say that the contour of the round pollen is never more irregular than that of the most irregular wrinkled peas, whilst that of the long pollen may be compared to a stout example of the dwarf bean Non Plus Ultra. Bateson crossed the long-pollened form of Emily Henderson with the short. *The result was a sweet pea of a deep purple colour*. The purple of the standard, the single outer erect petal, was of a redder shade than that of the wings, the two petals just below the standard. This sweet pea is known in the fancy as Purple Invincible, but is seen more often now in cottage gardens than in up-to-date collections. Its type of coloration is that of the original sweet pea as first brought into cultivation. The wild *Lathyrus odoratus*—of the Purple Invincible type—is common in Sicily. Here then is an extraordinary case of reversion. Two pure white sweet peas differing merely in the shape of their pollen are crossed, and a hybrid with the coloration of the ancestor of all cultivated sweet peas is the result. When these hybrids are allowed to self-fertilise, there results in F2 a variety of forms already well known to the fancy. These are: Purple Invincible again, Picotee, Painted Lady, and Tinged White and pure whites. Passing over the proportions in which the various coloured forms appear, there are found to be 9 coloured to 7 white.

Now, the 9 : 3 : 4 proportion in the culinary pea suggested the existence of two pairs of characters, one of which—the purple spot—could not be manifested in the absence of the other, the grey coat; though the grey coat could be manifested in the absence of the purple spot. The 9 : 7 is accounted for by supposing that colour in the sweet pea depends for its existence upon the simultaneous presence of two factors of distinct allelomorphic pairs, *neither of which* can be manifested in the absence of the other. These factors have been called C and R, their absences c and r respectively. If we write the familiar 9 : 3 : 3 : 1 scheme again, we get

9 C R, 3 cR, 3 Cr, 1 cr.

Only in the 9 C R are both C and R present; in the 3 cR and the 3 Cr only one of them is present, whilst in the 1 cr neither of them is. So that only the 9 are coloured and the remainder are all white.

The actual proportion of purples and reds and whites in F2 in this instance is 27 purple, 9 red, 28 white (= 36 coloured to 28 white, *i.e.* 9 coloured to 7 white). The existence and proportions of these reds are accounted for by calling in a new pair of allelomorphs, B and b. As already stated, colour is due to the meeting of C with R; if B is absent the colour is red, if present it is purple. But we will not deal further with this now.

Having now seen how these complicated cases of segregation, together with two instances of reversion, have been elucidated by Mendelian analysis, let us turn to other groups of the animal and vegetable kingdoms, and see what other characters have been dealt with in this way.

Except for the pair of allelomorphs with which we illustrated the simple Mendelian phenomenon, and for the very superficial reference to roundness and wrinkledness in peas, all the characters we have dealt with so far have been colour characters. But Mendelian inheritance is by no means confined to colour characters, as we shall shortly see. Perhaps one of the most striking instances of this is that studied by von Guaita, Weldon, and myself, the waltzing habit in mice. The waltzing habit characterises a race of mice known as Japanese waltzing mice, which have pink eyes and small patches of fawn on the shoulders and rump. A waltzing mouse does not always waltz, but can always be distinguished immediately from a normal mouse. The waltzing itself consists in merely spinning round and round very swiftly in one spot on all-fours. It is not in the least like waltzing. It is simply running round in a circle sometimes at a very great pace for several minutes at a time, so that all that you can see is a sort of nebulous ring of mouse. They do not always go round in the same direction,but sometimes in a right-handed direction, sometimes in a left. But when it is not waltzing, a waltzing mouse is immediately recognisable by the appearance of complete lack of control over the movements of its head, which is every now and again thrown back into an apparently very uncomfortable and useless attitude. A waltzing mouse also has the habit of running or rather shuffling backwards, waving his head vigorously from side to side the while. This mouse is said to have come originally from Japan. They certainly exist there now, but I have not been able to obtain any alive from that country. The depth of the ignorance of the general public concerning the simplest facts of heredity is shown by the fact that the following story of the origin of the waltzing mouse has been printed in a daily paper and, presumably, believed. "A mouse fancier once caught the head of one of his pets in the door of his cage. The mouse nearly died, but on recovery exhibited the waltzing movements now so familiar. Wishing to perpetuate the curiosity, the owner of the mouse carefully preserved and bred from the anomaly, and so originated the breed of waltzing mice!" What actually happened was probably that the feature arose as a sport which was carefully preserved and bred from. Waltzing is, in fact, a very good example of the kind of character that can arise in a tame breed, and be preserved because it tickles the fancy of man. Nature does not tolerate curiosities of this kind for a moment, and promptly eliminates them. The abnormality is due, not, as was originally believed, to the absence or atrophy of one of the semicircular canals, which have been demonstrated to be all there, but to a deficiency in their nerve supply. The waltzing is a constant character of the race; the children of waltzing mice mated together being all waltzers.

When such a waltzing mouse is mated with a normal mouse—with an ordinary white mouse, for example—the hybrid obtained is always *normal*, like the white mouse. Waltzing, therefore, is recessive, in the Mendelian sense, to normality of progression. In F2 we should expect the waltzing to reappear in the proportion of 25 per cent. of the whole fraternity. Reappear it certainly does, but not quite in the proportion expected. The number of waltzers, indeed, falls below 20 per cent., in the many hundreds of F2 mice which I have raised. I do not think that this deficiency is due to any complication of the process of segregation in the germ-cells, but believe it is merely due to the greater mortality which almost certainly takes place among waltzing individuals than among normal ones between the time when they are born and the age—from ten days to two weeks—when the characters of the mice are first registered. Waltzers are much more delicate than normal mice; and it is likely that this delicacy is more fatal in youth (perhaps even before birth) than in middle age.

The mice afford an excellent example of reversion. The Japanese waltzing mouse is almost an albino, and would be were it not for the patches of fawn-coloured fur on the shoulders and haunches. It has pink eyes. It was crossed with an albino mouse. The result, where the albino used was a pure-bred one, was a mouse hardly distinguishable at first sight from the common house mouse. A closer inspection reveals the lighter colour of the belly. Their eyes are jet black. And this is the most remarkable feature of the cross —the production of a black-eyed form from two parent forms both of which had pink eyes. These hybrids are not merely wild in their coloration, but are always noticeably healthier, stronger, and wilder than their albino parent, and infinitely more so than their waltzing parent. As already stated, they never waltz. When they are mated together they produce a generation which is composed of the three colour categories we have just mentioned in the proportions indicated by the percentages prefixed to them—viz. 25 per cent. pink eye and coloured coat (that of the Japanese waltzer), 50 per cent. dark eye and coloured coat (that of the hybrid), and 25 per cent. pink eye and colourless coat (*i.e.* complete absence of pigment or albinism.) The distribution of waltzing over these various colour categories is interesting. It is distributed, as it were, at random—that is to say, the waltzing character is not necessarily associated with that colour category with which it was associated in the pure waltzer, but may be associated with any of the three colour categories. So that we get in F2, besides waltzers coloured like their pure grandparents, waltzers with the black eyes and the grey coat of the house mouse, and albino waltzers. It may be noted in passing that these albino waltzers correspond to the green wrinkled peas we have already discussed—that is to say, they represent the association in F2 of the recessive character of one parent with the recessive character of the other parent in one individual which, since both characters it bears are recessive, may be counted on to breed true. It does.

Another illustration of a character other than colour is that which has been studied by Mr. R. H. Biffen. One of the most disastrous pestilences which affect the wheat is the fungoid pest known as Yellow Rust (*Puccinia glumarum*). Some varieties of wheat are more susceptible to it than others; for example, the variety Michigan Bronze is hardly ever free from it. Another variety grown by Mr. Biffen may be regarded as practically immune, for, although it was grown for four years in close proximity to the most rust-stricken varieties, it was not affected by the disease. This immune variety was crossed with Michigan Bronze. The hybrids were all so badly affected by the disease that one could not find an area an eighth of an inch square unattacked by the rust. No difference in respect of their susceptibility to the disease could be discerned between the hybrid and Michigan Bronze. But the hybrid did differ from it by the fact that whereas the susceptible parent hardly set a grain, the hybrid gave a moderate crop.

"Every available grain was sown in plots alongside the parent varieties, part on land which had been exhausted on a previous crop of wheat, and part on land which had carried a crop of clover the previous season and consequently was in high condition. The difference in cultivation, however, made no difference in the results of the experiment. The rust was late in appearing that season, but again every plant of the susceptible parent was stricken, and all of the immune type escaped entirely. The hybrid plots were badly attacked, and when the epidemic seemed to be well advanced, the plants were sorted into two groups—namely, those which were attacked, and those showing no signs of the disease even on the withering basal leaves. On some plots the diseased plants were cut out, leaving those free from infection for a subsequent examination. A few individuals, which had escaped the attack at the early stage, became infected later, and these were then added to the total of susceptible plants. The statistics showed that 1,609 diseased plants were present and 523 immune, or a ratio of 3·07 : 1. There cannot, I believe, be any question that these latter were really immune, for they were surrounded by plants covered in rust, whose leaves were continually rubbing against them. Further, if a variety is susceptible, no plant of it under field conditions ever appears to escape."[1]

Mr. Biffen concludes with the following remark: "Of the problems this opens up to the pathologist, nothing need be said here: for the present we are concerned with plant improvement, and it need only be noted that, according to the report of the International Phytological Bureau in 1890, the attacks of rust cost Germany some £20,000,000 sterling. Such figures give one some idea of the stakes the plant-breeder can now play for, and, thanks to the work of Mendel, with the reasonable certainty of winning."

But it is not merely by the discovery of facts of this kind that Mendelism is of service to the breeder of animals and plants.

Mendel and his followers have already put into the hands of breeders general principles of the greatest value. For example, those whose business is to breed cattle or carnations, or whose hobby is to breed fancy mice or sweet peas, and strive to improve their strains by crossing, are likely to be disappointed if they expect anything new in their first crosses. What could be more discouraging than to obtain a house mouse by crossing the delicate little waltzing mouse with the albino? And yet I have raised an entirely new colour—lilac, as it is called—by mating these hybrids together. Similarly in sweet peas the production of the original wild type of that flower by crossing two of the most beautiful modern strains would not tempt one to repeat the experiment. Mendelian principles drive home the lesson that we must expect nothing in the way of novelty from the first generation, and that it is on the next one that we must concentrate our attention.

Another extremely valuable instrument which Mendel has put into the hand of the breeder is the power of effecting the combination in one strain of desirable characters existing in separate strains, with great swiftness and precision. If the two characters we wish to combine are recessive ones, our task is an easy one, for we can effect their association in 1 individual in every 16 in the F2 generation. If, however, it is a dominant one, we have to wait till the following generation in order to determine which of the individuals bearing the dominant character are heterozygotes and which homozygotes.

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[1] Royal Horticultural Society, Third International Conference on Genetics, p. 376.

But we need not multiply instances. It must be sufficiently evident that the value of the tool which has been put into the hand of the breeder of animals and plants is such as can hardly yet be estimated.

Having now given examples of some of the more salient hereditary phenomena with which the Mendelian has been able to deal, and having made a brief reference to the economical importance of by-products of Mendelian investigation, we must resume the thread of the story and see whither it leads.

The culmination of Mendelian speculation is reached in the suggestion—for it is no more than that at present—that the inheritance of sex is Mendelian; that "male" and "female" represent two allelomorphs of a pair, like yellowness and greenness in peas. Sex certainly is a character which is inherited alternatively—that is to say, in organisms in which bi-sexual reproduction is the rule, an individual exhibits either the character of one parent or that of the other, but never a mixture of the two. It is a male or a female. But there is one profound difference between the hereditary relationship of the two characters, male and female, and the two characters, yellow and green; in the latter, one character (yellow) is always dominant over the other (green), in the former this is manifestly not the case. Let us see how the matter is dealt with by Castle, who was the first to formulate definitely the theory of the Mendelian inheritance of sex in a paper entitled "The Heredity of Sex."[1] He supposes that half of the germ-cells of every male individual contain the unit character "male," and half the unit character "female"; and that the germ-cells of females are similarly constituted. Now the result of the random union of a number of such spermatozoa and ova would be: 25 per cent. ♂♂ zygotes, 50 per cent. ♀♂, and 25 per cent. ♀♀. We see at once that all the homozygotes—the ♂♂s and the ♀♀s—if they mated with their like (*i.e.* ♀♀ with ♀♀, or ♂♂ with ♂♂) would be capable of producing members *of one sex only.* This difficulty is got over by saying that there is no reason to suppose that such sexually pure—*i.e.* homozygous—individuals exist; and Prof. Castle quotes cases which tend to show that in reality every organism, whether male or female, is potentially a hermaphrodite, and possesses the characters of the opposite sex to that to which it belongs in a latent state. It is well known that the removal of the generative organs of an animal often results in the appearance of the secondary sexual characters of the opposite sex; for example, the human eunuch has the high voice and the distribution of fatty tissue which is characteristic of the female. The most decisive case is perhaps that which is cited by Darwin, who relates that when the domestic cock is crossed with the hen pheasant, those of the offspring which happen to be males *have the secondary sexual characters of the male pheasant.* There is abundant evidence over and above that cited by Prof. Castle for the truth of his contention that members of both sexes are potentially hermaphrodite. So high an authority as Dr. Curt Herbst concludes, after an exhaustive scrutiny of a great mass of evidence, first, that the presence in a functional state of the generative organs of a particular sex are an indispensable condition for the elaboration of the secondary sexual characters of that sex; and, secondly, that the functional generative organ exercises a negative influence—*preventing the appearance of the secondary sexual characters of the opposite sex.*[1]

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[1] *Mus. Comp. Zool. Harvard*, vol. xl. No. 4.

To return therefore to our argument, Prof. Castle contends—and we have seen that his contention is supported by independent evidence—that the individuals of a normally bi-sexual species are not sexually pure, but potentially hermaphrodite. From this he concludes that the homozygous individuals ♀♀ and ♂♂ do not exist. He accounts for their non-existence by supposing that the unions between ova and spermatozoa bearing similar sexes are infertile. And he adduces evidence, other than the *a priori* considerations we have spoken of, for this view. Only half the unions are fertile, namely, those between ova and spermatozoa bearing dissimilar sexes. And, in this way, only heterozygotes are produced which are capable of producing both sexes. Furthermore, to account for the fact that half of these heterozygotes display the male and half the female primary and sexual characters, we have to suppose that in the case of the allelomorphic pair "male" and "female," we have alternative dominance of either of the pair, as opposed to the fixed dominance of one of the pair which obtains in the ordinary Mendelian pairs.

We have stated that it has been shown that the characters of one sex are latent in the opposite one. It is extremely important that this phrase "latent" should not be misconstrued. The manner in which the Mendelians picture this "latency" is to suppose that the members of both sexes are heterozygotes, half of whose germ-cells contain the male character and half the female character. They do *not* believe—and this is the essence of the Mendelian doctrine of gametic purity—that the germ-cell which produces a female contains maleness as well. Maleness would only be admitted to be latent in a woman in the sense that greenness is latent in a cross between a green and a yellow pea.

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[1] *Formative Reize*, p. 76.

There is another sense in which the phrase *latent* is used which must not be misconstrued. When a grey-skinned was crossed with a white-skinned pea, the hybrids, which were grey with purple spots, gave in F2 nine greys with purple spots, three greys, and four whites, three of which, it will be remembered, were whites carrying purple spots, which was not manifested because the grey was absent. Bateson protests against the statement that purple spot is latent in these whites. "Sulphate of copper," he says, "is blue and chloride of copper is green, but it would be improper to speak of blue as latent in sulphuric acid, or of green as latent in hydrochloric acid."

STEREO-CHEMISTRY AND ITS APPLICATION TO PHYSIOLOGY

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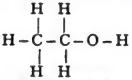
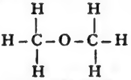
When two substances contain equal numbers of similar atoms and yet show a difference in properties, they are said to be *isomeric*. In the great majority of cases isomerism is due to a structural difference between the compounds in question—*i.e.* though they are made up of the same atoms, these atoms are differently linked together in the several substances. For example, ethyl alcohol and dimethyl ether are isomeric substances, both having the formula C_2H_6O; in the alcohol the oxygen atom links together a carbon and a hydrogen atom, while in the other case it unites two carbon atoms:



$$H-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-O-H$$

Ethyl alcohol.



$$H-\overset{H}{\underset{H}{C}}-O-\overset{H}{\underset{H}{C}}-H$$

Dimethyl ether.

This view sufficed for a time to explain nearly every case of isomerism known; but as more and more facts were accumulated, it became evident that some examples of isomerism could not be classed under this head; for compounds were discovered whose structures were identical, while very considerable differences were found in their properties. Organic chemists were thus forced to seek some new explanation for these phenomena.

It had been observed that several of these isomeric bodies had a peculiar influence on polarised light. It is well known that many crystalline compounds in the solid state will rotate the plane of polarisation of a polarised ray passed through the crystal; but since quartz possesses this property only when crystalline and not when in a state of amorphous silica, it is evident that we are dealing in its case merely with the influence of crystalline structure. But if we take a crystal of natural tartaric acid and dissolve it in water, so that it loses its crystalline form, we find that in solution it still has an action on the plane of polarisation. Similarly, camphor when fused does not lose its power of rotating the plane of polarisation, though it has lost its crystalline character. In the case of these substances, therefore, the influence exerted on the plane of polarisation is not due to the same cause as the rotatory power of the quartz crystal; it is rather to be sought within the molecule itself.

It has been found that these *optically active* substances exist in two forms, one of which rotates the plane of polarisation to the right, while the other isomer rotates it through an equal angle to the left. This has led to the adoption of the current nomenclature, wherein the name of the right-rotating substance has the prefix *dextro* attached to it, while the left-rotating variety is termed the *lævo* isomer. Thus we speak of dextro camphor and lævo camphor, or simply *d*-camphor and *l*-camphor. Now, obviously, if we mix equal quantities of the dextro and lævo isomer together, the resulting mixture will have no influence upon the plane of polarisation; for the action of the right-rotating substance will be counteracted by the equal and opposite effect of the left-rotating body, and the mixture will be inactive by *external compensation*. Under certain conditions it is found that the dextro and lævo molecules combine together to form an actual inactive compound, which is termed a *racemic* substance (usually abbreviated to *r* or *dl*). The dextro and lævo bodies are usually referred to as *optical antipodes*.

The first successful step in the study of these substances was made by Pasteur[1] in 1860, when he took up the question of the tartaric acids. He was able to show how to isolate the dextro and lævo forms from the racemic compound, discovering no fewer than three separate methods of attaining this object. He showed, further, that while racemic tartaric acid crystallizes in holohedral form, the dextro and lævo isomers show hemihedrism, the dextro crystal being the mirror image of the lævo crystal. A consideration of the general properties of the three substances led Pasteur to the conclusion that in the dextro and lævo forms the atoms might be grouped in spirals or situated at the corners of a tetrahedron. He was unable, in the elementary state of structural chemistry at that time, to do more than put this forward as a conjecture, and it remained for two later investigators to reap the credit of establishing the correctness of this view.

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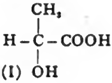
[1] Pasteur, *Recherches sur la dissymmétrie moléculaire des produits organiques naturels*, Paris (1860).

Pasteur believed that the optical activity of the tartaric acids was undoubtedly due to an asymmetric arrangement of which the right-handed form was the mirror image of the left-handed variety, just as a left-handed glove is a mirror image of a right-handed one. Thirteen years later, in 1873, Wislicenus[1] proved that active and inactive lactic acids had identical structures; and in his examination of the question, added, "The facts force us to explain the difference between isomeric molecules of similar structure by a different arrangement of atoms in space."

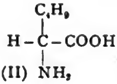
These suggestions did not lie dormant for any length of time, for in 1874 Le Bel[2] and van't Hoff[3] simultaneously and independently published papers in which the foundations of modern stereo-chemistry were laid.

Le Bel and van't Hoff pointed out that in every case where optical activity had been observed in a compound, the substance in question contained at least one *asymmetric carbon atom*, *i.e.* an atom whose four valencies are attached to four different radicles. Examples of this are found in lactic acid (i), leucine (ii), malic acid (iii), and amyl alcohol (iv), represented in the formulæ below, in each of which the asymmetric atom lies in the centre of the figure:



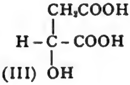
(I)

$$H-\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}-COOH$$



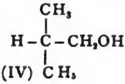
(II)

$$H-\overset{\displaystyle C_4H_9}{\underset{\displaystyle NH_2}{C}}-COOH$$



(III)

$$H-\overset{\displaystyle CH_2COOH}{\underset{\displaystyle OH}{C}}-COOH$$



(IV)

$$H-\overset{\displaystyle CH_3}{\underset{\displaystyle C\,H_5}{C}}-CH_2OH$$

In the literature of that time, some cases were recorded which conflicted with this view, but later work has proved them to be due to faulty observation, and the Le Bel-van't Hoff theory has been completely established.

Now, when we examine the problem in the light of this evidence, we find that it is at once simplified. We need only recur to Pasteur's view that atoms in optically active compounds are situated at the corners of a tetrahedron, and the matter becomes clear. Let us suppose that the asymmetric carbon atom is situated at the centre of a tetrahedon, and that the four groups attached to it lie at the tetrahedron's corners. In the case of lactic acid, we shall find that two arrangements are possible, each being the mirror image of the other:

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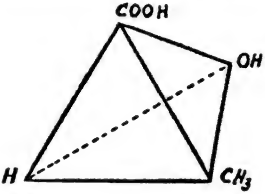
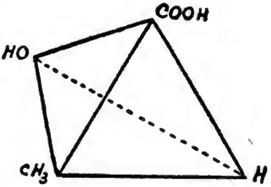
[1] Wislicenus, *Annalen der Chem.*, **167**, 343 (1873).

[2] Le Bel, *Bull. Soc. chim.*, [2], **22**, 377 (1874).

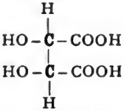
[3] van't Hoff, *Voorstell tot uitbreidung der structuur-formules in de ruimte*, Utrecht (1874).





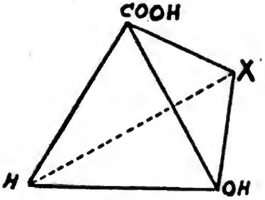
The two arrangements are unsuperposable, being related to one another as a man's right hand is to his left. Compounds which owe their difference to an arrangement of atoms in space are said to be *stereo-isomeric.*

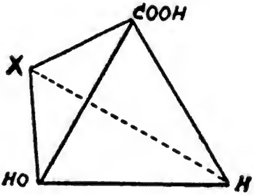
We must now consider the effect of introducing a second asymmetric carbon atom into the molecule. This was first observed by Pasteur in the researches on the tartaric acids which we have already mentioned. When we examine the structural formula of tartaric acid, we see that it contains two asymmetric carbon atoms, which are marked by heavy type:



$$\begin{array}{c} \mathrm{H} \\ | \\ \mathrm{HO-}\mathbf{C}\mathrm{-COOH} \\ | \\ \mathrm{HO-}\mathbf{C}\mathrm{-COOH} \\ | \\ \mathrm{H} \end{array}$$

If we divide the molecule into two halves of identical structure, $-\mathrm{CH(OH)COOH}$, we shall see that we have now three possible arrangements of atoms in space instead of two, as in the case of lactic acid. Instead of the second group $-\mathrm{CH(OH)COOH}$, let us write X for convenience; then, as before, we have the two arrangements:





These represent the right-handed and left-handed varieties of the grouping XCH(OH)COOH. But now we have still to consider the grouping of the atoms in X, the second radicle −CH(OH)COOH. They also may be arranged in dextro or lævo form. Now, if we call the rotatory power of the one half of the molecule A, we shall find that first we have

$$+A \qquad\qquad -A$$

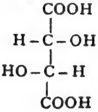
and to each of these we can add a dextro or a lævo form of the second half molecule, which has also a rotatory power, A. This gives us:

$$\begin{array}{cccc} +A & +A & -A & -A \\ +A & -A & +A & -A \\ (1) & (2) & (3) & (4) \end{array}$$

Form (1) and form (4) represent dextro- and lævo-rotatory bodies having a rotatory power of twice A. But when we examine forms (2) and (3) we find that they have no rotatory power at all, one half of the molecule counteracting the other half, just as one molecule of dextro camphor counteracts a molecule of lævo camphor and produces inactive camphor. The inactivity of the tartaric acid, however, depends upon compensation *within* the molecule itself, and the case is said to be one of *internal compensation.* Internally compensated tartaric acid is usually termed meso-tartaric for the sake of convenience.

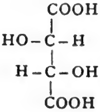
The tetrahedron symbol does not lend itself to easy reproduction in printing, so other means were devised to represent the *configuration* or space arrangement of atoms in a compound. The method suggested by Fischer is the most generally employed. To use his formulæ, the tetrahedron model is first supposed to be built up in the usual way; and then, after laying it on a sheet of paper, the positions of the groups of atoms are projected upon the paper. As an example, we may draw the formulæ of the tartaric acids, giving a sketch of the tetrahedra in each case:

1. **d**-tartaric.



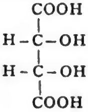
$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{H-C-OH} \\ | \\ \mathrm{HO-C-H} \\ | \\ \mathrm{COOH} \end{array}$$

2. **l**-tartaric.

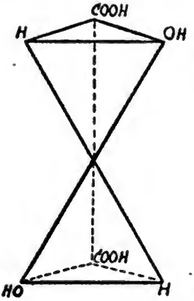


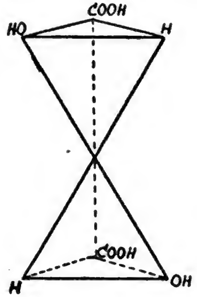
$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{HO-C-H} \\ | \\ \mathrm{H-C-OH} \\ | \\ \mathrm{COOH} \end{array}$$

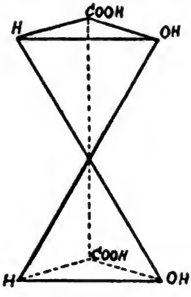
3. Meso-tartaric.



$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{H-C-OH} \\ | \\ \mathrm{H-C-OH} \\ | \\ \mathrm{COOH} \end{array}$$







An equimolecular mixture of (1) and (2) gives racemic acid.

One point must be noticed. It might be supposed that if the two tetrahedra in the tartaric acids were to revolve around their common axis, the one isomer could be changed into the other, but this is not the case. The configuration of each isomer depends upon the *order* in which the groups are disposed around the tetrahedron, and no revolution can alter this. It is assumed that in these isomers the two tetrahedra can vibrate quite freely; but it is probable that, under any given conditions, they will come into equilibrium in some fixed position.

In order to make clear the difference in physical properties which is produced by differences in the arrangements of atoms in space, a table is given below which includes the chief properties of the dextro, lævo, meso, and racemic forms of tartaric acid:

	Dextro	Lævo	Meso	Racemic
Melting-point	170°	170°	140°	206°
Affinity Constant . .	0·097	0·097	0·060	0·097[1]
Specific Gravity . .	1·755	1·754	1·666	1·697
Solubility in 100 parts of water at 15° .	136	136	125	17

We must now consider what influence is exerted upon certain reactions by these differences in the spacial arrangements of atoms; and, in the first instance, we may deal with the actions of certain organisms upon racemic compounds. It has been observed by many observers,[2] of whom Pasteur was the pioneer, that when moulds of various kinds were allowed to grow in a racemic solution to which phosphates or other nutrient matter had been added, the solution gradually became optically active, an excess of one antipode being left. At one time it was supposed that the mould was unable to attack one antipode, and confined its destructive action entirely to the other; but the work of Frankland and MacGregor,[1] and of McKenzie and Harden,[2] showed this to be erroneous; the mould destroys both antipodes, but appears able to attack one much more rapidly than the other. This difference in action must be due to the difference in configuration between the two antipodes. Since some moulds attack the dextro form while others destroy the lævo variety, it is possible to obtain either the left-handed or the right-handed form of a given body by utilising the appropriate mould. For instance, if we treat racemic mandelic acid with the ferment *Penicillium glaucum*, an excess of dextro mandelic acid results, while lævo mandelic is obtained by using *Saccharomyces ellipsoideus*. Fischer and Thierfelder[3] have noted another case of fermentation in which even a slight difference in the configuration appears to exert a considerable influence. They treated the dextro forms of glucose, mannose, galactose, and talose with the same ferment, and found that while the first two were easily fermented, galactose was attacked only with difficulty, while talose was not affected. When we examine the space formulæ of the four bodies, a possible explanation of this difference suggests itself:

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[1] This is probably not the true value for K, as in dilute solutions the racemic acid dissociates into the two antipodes.

[2] A complete set of references is to be found in Landolt's *Optische Drehungsvermögen organischer Substanzen*, Brunswick; or in Winther, *Ber.*, **28**, 3022 (1895).

Glucose	Mannose	Galactose	Talose
CH_2OH	CH_2OH	CH_2OH	CH_2OH
HO.H	HO.H	HO.H	HO.H
HO.H	HO.H	H.OH	H.OH
H.OH	H.OH	H.OH	H.OH
HO.H	H.OH	HO.H	H.OH
CHO	CHO	CHO	CHO
Ferment easily.		Fermentable	Unfermented.

Fischer supposes that ferment and sugar fit each other as a key fits a lock; so that certain "wards" of the sugar can be reached only if the ferment has a configuration similar to that of the sugar. If we symbolise part of the ferment in the same way as the sugars, and represent by X the "ward" which touches the hydroxyl group, we shall find that a perfect ferment for glucose would be written thus:

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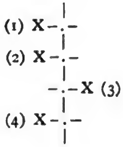
[1] Frankland and MacGregor, *Journ. Chem. Soc.*, **63**, 1034 (1893).

[2] McKenzie and Harden, *Journ. Chem. Soc.*, **83**, 424 (1903).

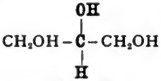
[3] Fischer and Thierfelder, *Ber.*, **27**, 2035 (1894).



$$\begin{array}{rcl} & | & \\ (1)\ X- & . & - \\ & | & \\ (2)\ X- & . & - \\ & | & \\ - & . & -X\ (3) \\ & | & \\ (4)\ X- & . & - \\ & | & \end{array}$$

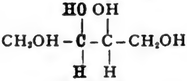
Here four "wards" come into play. In the case of mannose, only three of these (1, 2, and 3) are able to act; in galactose, 1, 3, and 4 would be able to attack the hydroxyl groups; while in talose only two (1 and 3) could come into action. This analogy of lock and key must not be pushed too far, but there certainly appears to be some relation between configuration and the ease of fermentation in certain compounds.

Results of a somewhat similar nature were obtained by Bertrand[1] in his studies of the action of the sorbose bacterium (*Bacterium xylinum*) on certain polyhydric alcohols. He found that the following alcohols were attacked by the organism:



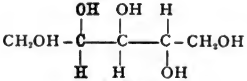
$$\begin{array}{ccc} & \mathbf{OH} & \\ & | & \\ CH_2OH- & \mathbf{C} & -CH_2OH \\ & | & \\ & \mathbf{H} & \end{array}$$

Glycerol



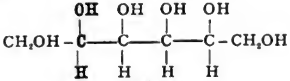
$$\begin{array}{ccccc} & \mathbf{HO} & & OH & \\ & | & & | & \\ CH_2OH- & \mathbf{C} & - & C & -CH_2OH \\ & | & & | & \\ & \mathbf{H} & & H & \end{array}$$

Erythritol



$$\begin{array}{ccccccc} & \mathbf{OH} & & OH & & H & \\ & | & & | & & | & \\ CH_2OH- & \mathbf{C} & — & C & — & C & -CH_2OH \\ & | & & | & & | & \\ & \mathbf{H} & & H & & OH & \end{array}$$

Arabitol

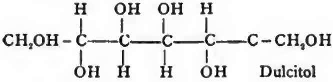


$$\begin{array}{ccccccccc} & \mathbf{OH} & & OH & & OH & & OH & \\ & | & & | & & | & & | & \\ CH_2OH- & \mathbf{C} & — & C & — & C & — & C & -CH_2OH \\ & | & & | & & | & & | & \\ & \mathbf{H} & & H & & H & & H & \end{array}$$

Sorbitol

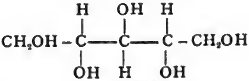
In each ease the heavily printed $-CHOH-$ group is oxidised to $-CO-$. On the other hand, compounds such as those below are not attacked in this way:

Glycol
CH_2OH-CH_2OH



$$\begin{array}{ccccccccccc} & H & & OH & & OH & & H & & & \\ & | & & | & & | & & | & & & \\ CH_2OH- & C & — & C & — & C & — & C & — & C & -CH_2OH \\ & | & & | & & | & & | & & & \\ & OH & & H & & H & & OH & & & \end{array}$$

Dulcitol



$$\begin{array}{ccccccc} & H & & OH & & H & \\ & | & & | & & | & \\ CH_2OH- & C & — & C & — & C & -CH_2OH \\ & | & & | & & | & \\ & OH & & H & & OH & \end{array}$$

Xylitol

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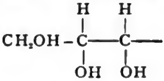
[1] Bertrand, *Bull. Soc. chim.*, [3], **19**, 347, 947, 999 (1898); *Compt. rend.*, **122**, 900 (1896); **126**, 762 (1898).

An examination of the formulæ shows that two conditions must be fulfilled before the bacterium can act. In the first place, the compound must contain a $-CHOH-$ group next a $-CH_2OH$ radicle; and in the second place it must have a space formula in which two hydroxyl groups lie next each other. In other words, unless a compound contains the grouping



$$CH_2OH-\underset{OH}{\overset{H}{\underset{|}{\overset{|}{C}}}}-\underset{OH}{\overset{H}{\underset{|}{\overset{|}{C}}}}-$$

the bacterium cannot attack it.

The foregoing results are sufficient to show that an intimate relationship exists between the molecular configuration of substances and the readiness with which they are attacked by ferments. Since this relationship exists in these cases, it is natural to expect a similar connection between the configuration of a substance and its behaviour in the bodies of animals. A large portion of all animal tissue is made up of asymmetric substances, and it appears probable that if an optically active substance is digested, either the dextro or the lævo form will react more easily than its antipode during the process.

When we consider the case of the three possible substances (dextro, lævo, and racemic), and suppose for the sake of convenience that the dextro compound is more easily assimilated than the lævo antipode by a given animal, we shall find that the racemic substance offers a further peculiarity; for if it passes through the organism as an actual compound, both its components will be destroyed to a certain equal extent, while if it breaks down into a mixture of its constituents, the dextro form will be attacked while the lævo isomer is unassimilated. We shall meet several cases of this kind in the work about to be described.

The simplest case of all is that of the tartaric acids, which has been described by Brion.[1] He found that racemic acid was least oxidised in the animal organism; next came dextro tartaric; while lævo tartaric and meso tartaric were most strongly acted upon. This proves that racemic acid, in its passage through the organism, is not decomposed into a mixture of dextro and lævo forms; as in that case the lævo form would be destroyed and a preponderance of the dextro form would remain.

[1] Brion, *Zeit. physiol. Chem.*, **25**, 283 (1898).

Further, the action of the animal tissue upon meso tartaric acid can be explained in the following way. Lævo tartaric acid is made up of two radicles, $-CH(OH)COOH$, each of which is arranged in lævo configuration, which is favourable to the attack of the organism; dextro tartaric acid, being composed of two dextro radicles, $-CH(OH)COOH$, offers no foothold to the destructive action of the tissues: the meso form, being made up of one dextro and one lævo radicle, offers a point of attack in the latter, and is therefore destroyed.

Neuberg and his collaborators have studied that part of the subject, and have examined several cases of the behaviour of optical antipodes in the animal body. We may take the case of the three arabinoses and their derivatives[1] as an example. The arabinoses are sugars which have the structural formula $CH_2OH.CH(OH).CH(OH).CH(OH).CHO$. The figures below represent in each case the percentage of substance recovered from the urine of rabbits; column I shows the results obtained when the substance was introduced through the mouth, II when introduced subcutaneously, and III intravenously:

	I	II	III
Lævo arabinose	14·5	7·1	28·3
Racemic arabinose	28·5	31·7	29·0
Dextro arabinose	31·2	36·0	31·0

These results agree fairly well among themselves, when allowance is made for inevitable experimental differences. The three sodium salts of the arabonic acids, $CH_2OH.CHOH.CHOH.CHOH.COONa$, show similar differences, though less of the lævo than of the dextro isomer is attacked in their case. When the corresponding alcohol arabite, $CH_2OH.CHOH.CHOH.CHOH.CH_2OH$, was supplied to the animal, small quantities of pentoses, $CH_2OH.CHOH.CHOH.CHOH.CHO$, appeared in the urine, one of the $-CH_2OH$ groups at the end of the chain being oxidised to $-CHO$.

A very important result was obtained by Neuberg and Wohlgemuth[2] in the case of the human subject. In certain diseases it is found that *racemic* arabinose makes its appearance. Now, when racemic arabinose was supplied to a human subject it was found that a considerable action took place, about two-thirds of the excreted substance being in the active form, showing that the racemic compound had been broken down into its components, one of which had been destroyed. It is therefore obvious that the formation of racemic arabinose due to disease must take place in an organ so situated that after being liberated from it the arabinose is not submitted to any process of decomposition.

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[1] Neuberg and Wohlgemuth, *Ber.*, **34**, 1745 (1901); *Zeit. physiol. Chem.*, **35**, 41 (1902).

[2] *Ibid.*

Since a difference in configuration such as exists between dextro and lævo forms has such a pronounced effect on the nutritive values of the arabinoses, it is not astonishing that Nagano[1] found a similar difference between lævo xylose and lævo arabinose, the former being more easily absorbed by the system. The configuration formulæ of the two substances are shown below.

l-Xylose	l-Arabinose
CH_2OH	CH_2OH
HO.H	H.OH
H.OH	H.OH
HO.H	HO.H
CHO	CHO

Analogous results were obtained by Neuberg and Meyer[2] in the case of the mannoses, $CH_2OH.CHOH.CHOH.CHOH.CHOH.CHO$. The dextro form appeared best suited for nutrition. The chief point of interest for stereochemical workers lies in the fact that during the passage of the dextro, lævo and racemic compounds through the system derivatives of another sugar, glucose, were produced. The formulæ of *d*-mannose and *d*-glucose are given below.

d-Mannose	d-Glucose
CH_2OH	CH_2OH
HO.H	HO.H
HO.H	HO.H
H.OH	H.OH
H.OH	HO.H
CHO	CHO

As can be seen from an inspection of the formulæ, the change from mannose to glucose necessitates the rearrangement of the groups attached to the lowest carbon atom in the formula. Such a rearrangement implies no great strain on the molecular arrangement, however, as it may be supposed to take place by a wandering of a hydrogen atom, thus:

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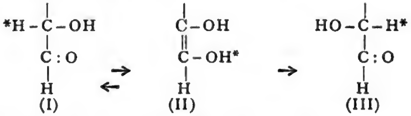
[1] Nagano, *Pfluger's Archiv.*, **90**, 389 (1902).

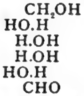
[2] Neuberg and Meyer, *Zeit. physiol. Chem.*, **37**, 530 (1903).



$$\begin{array}{c} | \\ {}^{*}H-C-OH \\ | \\ C:O \\ | \\ H \\ \text{(I)} \end{array} \quad \begin{array}{c} \rightarrow \\ \leftarrow \end{array} \quad \begin{array}{c} | \\ C-OH \\ \| \\ C-OH^{*} \\ | \\ H \\ \text{(II)} \end{array} \quad \rightarrow \quad \begin{array}{c} | \\ HO-C-H^{*} \\ | \\ C:O \\ | \\ H \\ \text{(III)} \end{array}$$

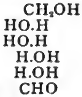
The form (II) is unstable. If a model be built up to represent these formulæ, it will be found that when the hydrogen atom marked with an asterisk wanders back from the position (II) it may give rise to (I) or (III). The action of the living tissues in this case is evidently exerted to bring about the change of (II) into (III) rather than of (II) into (I).

Rosenfeld[1] has found that sugars are excreted in urine in the following order: galactose, mannose, glucose; while the alcohols follow the analogous order: dulcite, mannite, sorbite.



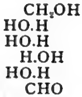
$$\begin{array}{c} CH_2OH \\ HO.H \\ H.OH \\ H.OH \\ HO.H \\ CHO \end{array}$$

d-Galactose



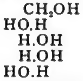
$$\begin{array}{c} CH_2OH \\ HO.H \\ HO.H \\ H.OH \\ H.OH \\ CHO \end{array}$$

d-Mannose



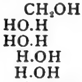
$$\begin{array}{c} CH_2OH \\ HO.H \\ HO.H \\ H.OH \\ HO.H \\ CHO \end{array}$$

d-Glucose



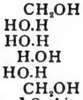
$$\begin{array}{c} CH_2OH \\ HO.H \\ H.OH \\ H.OH \\ HO.H \\ CH\ OH \end{array}$$

Dulcite



$$\begin{array}{c} CH_2OH \\ HO.H \\ HO.H \\ H.OH \\ H.OH \\ CH_2OH \end{array}$$

d-Mannite



$$\begin{array}{c} CH_2OH \\ HO.H \\ HO.H \\ H.OH \\ HO.H \\ CH_2OH \end{array}$$

d-Sorbite

These differences are probably caused by some reaction similar to that which takes place in the selective fermentation of certain sugars, which was described above.

Having dealt with the influence of the configuration of optical antipodes upon their nutritive value, we must turn to another side of the question, and consider the relations between the configurations and toxic qualities of various compounds. No general rule can be laid down in this case; for, as in the case of nutrition, the experimental data are here far too meagre to allow of generalisation.

In the first place, it is advisable to point out that in some cases influences intervene which are only indirectly attributable to the special arrangement of atoms in space. For example, Chabrié's[1] experiments on the toxicity of the tartaric acids are stated by Cushny[2] to be unreliable, as the toxic agent in this case is really the hydrogen ion and not the acid itself. Since the configuration of the acid's molecule influences its ionization, however, it should in this way have some effect upon its toxicity also. Chabrié's figures are given below. They are calculated in the following way: Let x be the weight of acid required to kill one kilogram weight of an animal in one minute, p the weight of acid, and w the weight of animal used, and T the time required to kill determined by experiment, then

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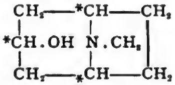
[1] Rosenfeld, *Centralblatt f. innere Medicin*, **21**, 177 (1900).

$$\frac{1}{x} = \frac{1000\,p.\,T}{w}$$

	$\frac{1}{x}$
Lævo-tartaric acid	34·26
Dextro „ „	104·24
Racemic acid	165·25
Meso-tartaric acid	196·27

It will be seen from a comparison of these figures with Brion's results, which have already been given, that there is no close connection between the two.

Owing to their applications in medicine, the behaviour of compounds of the tropine series has been investigated with more thoroughness than that of other isomers. The parent substance, tropine, has the following structure:



in which three carbon atoms (marked with asterisks) are asymmetric. When tropine (melting-point 62°) is treated with sodium amylate, it is converted into an isomeric body, pseudotropine (melting-point 108°). The two compounds have exactly the same structure, and the difference between them is due, probably, to the different arrangement of the —CH.OH— radicle. Ladenburg[3] has suggested another explanation depending upon the special arrangement of groups around the nitrogen atom. Whichever be true, the isomerism of tropine and pseudo-tropine is caused by spacial, not structural differences. When we allow mandelic acid to react with the hydroxyl groups of tropine and pseudo-tropine, we obtain two stereoisomeric esters, each of which has the following structure:

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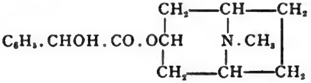
[1] Chabrié, *Compt. rend.*, **116**, 1410 (1893).

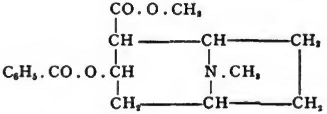
[2] Cushny, *Journ. Physiol.*, **30**, 193 (1904).

[3] See Ladenburg, *Ber.*, **26**, 854 (1893); **36**, 3694 (1903); and Groschuff, *ibid.* **34**, 2974 (1904), for examples of this type of isomerism.



The ester obtained from tropine has a strong mydriatic action, while the pseudo-tropine ester has no such property.

When one of the hydrogen atoms of tropine is replaced by a carboxyl group, tropine carboxylic acid is formed; and when the alcoholic radicle of this substance is benzoylated while the carboxyl group is esterified with methyl alcohol, we obtain cocaine, which has the formula:



Cocaine, of course, since it contains asymmetric carbon atoms, exists in two antipodic forms of equal and opposite rotatory power. Poulsson[1] found that when applied to the tongue the paralysing action of dextro cocaine was stronger and set in more rapidly than that of lævo cocaine; but, on the other hand, the effect of the dextro isomer was not so permanent as that of the lævo antipode. In the case of rabbits and frogs, the fatal dose seems to be the same for each isomer. Ehrlich and Einhorn[2] arrived at similar results.

According to Hesse[3] the therapeutic action of scopolamine and the corresponding racemic compound atroscine differ from each other.

Cushny[4] investigated the actions of lævo hyoscyamine and atropine, which is the corresponding racemic form. These substances are the tropine esters of tropic acid, and have the formula :

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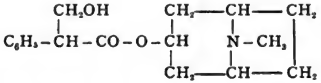
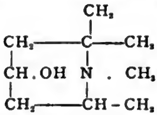
[1] Poulsson, *Archiv exp. Path. u. Pharmak.*, **27**, 309 (1890).
[2] Ehrlich and Einhorn, *Ber.*, **27**, 1870 (1894).
[3] Hesse, *Journ. f. prakt. Chem.*, [2], **64**, 353 (1901).
[4] Cushny, *Journ. Physiol.*, **30**, 193 (1904).



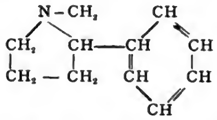
It was found that both atropine and *l*-hyoscyamine have the same action upon the central nervous system of animals, the effects being not only qualitatively but also quantitively identical. When applied to the spinal cord reflexes, atropine has a more powerful influence than the active isomer; but this is reversed in the case of the nerve ends of the heart, the salivary glands, or the pupil of the eye; for at each of these points *l*-hyoscyamine has an effect twice as strong as that produced by atropine. From these results we can deduce the probable effect of dextro hyoscyamine. We know that *dl*-hyoscyamine (atropine) has the same effect as *l*-hyoscyamine on the central nerve system of mammals; therefore in this case dextro and lævo forms must have the same effect. But, on the other hand, *dl*-hyoscyamine has a greater effect than *l*-hyoscyamine on the spinal cord, so that here, obviously, *d*-hyoscyamine must exert a greater influence than *l*-hyoscyamine. In the case of the heart, the effects are again reversed; for since here *l*-hyoscyamine is twice as powerful as *dl*-hyoscyamine, it appears that *d*-hyoscyamine must be almost without action. Of course this reasoning assumes that the racemic compound breaks up into the two antipodes before it acts upon the various nerves.

Two other substances should now be described, as they are closely allied to the tropine group. If in the formula of tropine we replace the radicle —CH_2—CH_2— by two methyl groups, and at the same time exchange a hydrogen atom of a —CH— group for a methyl radicle, we obtain the following formula, which represents N-methyl-vinyl-diacetone-alkamine :



Like tropine itself, this compound exists in two isomeric forms, the mandelic ester of one being an oil, while that of the other melts at 113°. In this case also the labile isomer has a mydriatic action, while the stable isomer lacks that property.

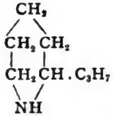
The actions of the two antipodic forms of nicotine:



have been studied by Mayor,[1] who found that the lævo form was twice as poisonous as the other. When dextro nicotine is injected no pain is felt; but when the lævo isomer is used it produces both pain and excitation. The lævo antipode causes paralysis, spasms, retardation of the action of the heart, and finally death by the cessation of respiration; while the same dose of dextro nicotine produces only a strong shivering fit, which soon passes off.

Only one or two other cases need be mentioned in this division of the subject. Albertoni[2] has shown that the dextrorotatory compound cinchonine differs in action from its lævorotatory isomer cinchonidine. The latter has a slower action, requires a larger dose to produce the same effect as the dextro isomer, gives rise to vomiting, and has a marked tendency to cause spasms. Quinine and quinidine, which are also optical isomers, differ in physiological action as well, quinidine having no narcotic properties, though showing the febrifugial action of quinine.

Coniine has the structure:



and as it contains an asymmetric carbon atom it occurs in active and racemic forms. Ladenburg and Falk[3] compared the action of the dextro antipode with that of the racemic form, but were unable to detect any difference between the two effects.

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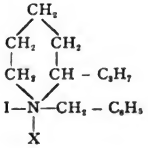
[1] Mayor, *Ber.*, **38**, 597 (1905).

[2] Albertoni, *Archiv exp. Path. u. Pharmak.*, **15**, 272.

[3] Ladenburg and Falk, *Annalen d. Chem.*, **247**, 83 (1888).

Hildebrandt,[1] examining ethyl, propyl, butyl, and iso-amyl derivatives of benzyl-coninium iodide, found that the isomer with the lower melting-point had also the weaker physiological action. The general formula of these bodies is shown below, the position occupied by the ethyl, propyl, butyl or iso-amyl radicle being indicated by X.

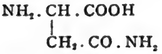


In the preceding paragraphs we have shown that the influence of the antipodic arrangement of atoms in a molecule is well marked in many cases. We must now mention several instances which show that differences in the configuration of compounds may affect our senses.

In the first place, we may point out that the crystals of the dextro and lævo forms of sodium ammonium tartrate differ from each other and from those of sodium ammonium racemate. The optically active compounds crystallise in hemihedral form, and the crystal of the *d*-salt is the mirror-image of that of the *l*-salt. The racemic salt exhibits no hemihedral faces in its crystals. The spacial arrangement of atoms, since it lies at the root of this difference in crystalline form, certainly affects our sense of touch.

Passing now to the question of smell, it has been found by Werner and Conrad[2] that the methyl esters of the two optically active trans-hexahydroterephthalic esters have different odours; while Schmidt and Tiemann observed that racemic terpenes were less odoriferous than the corresponding active isomers.

Taste, in its turn, is affected in the same way, for Piutti[3] states that the dextro and lævo forms of asparagine



$$\begin{array}{l} NH_2.\,CH.\,COOH \\ \qquad\;\; | \\ \qquad\; CH_2.\,CO.\,NH_2 \end{array}$$

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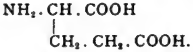
[1] Hildebrandt, *Ber.*, **38**, 597 (1905).

[2] Werner and Conrad, *Ber.*, **32**, 3052 (1899).

[3] Piutti, *Compt. rend.*, **103**, 134 (1886).

have different tastes, that of the *d*-form being sweet, while the *l*-isomer is insipid. Fischer and Hagenbach[1] state that lævo leucine has a weakly bitter taste, while the dextro form is quite sweet. A similar difference was noted by Menozzi and Appiani,[2] who found that *d*-glutaminic acid was sweet, while the lævo form was tasteless. Glutaminic acid has the formula:



$$\begin{array}{l} NH_2.CH.COOH \\ \qquad\;\, | \\ \qquad\; CH_2.CH_2.COOH. \end{array}$$

In the case of mannose and glucose, the evidence is conflicting; for van Ekenstein[3] states that mannose is sweet, while glucose is bitter; but this is contradicted by Neuberg and Mayer.[4] Sternberg[5] considers that as a rule the difference between the isomers is quantitative rather than qualitative. If this be correct, it opens up a field for speculation. Marckwald and McKenzie[6] have shown that when an active acid is esterified with a racemic alcohol, or *vice versâ*, the reaction proceeds faster with one component of the racemic body than with the other. For instance, they found that lævo menthol combines more rapidly with dextro-mandelic acid than with lævo-mandelic acid. If we recall that Pasteur conceived nerves as asymmetric organisms, the "quantitative difference" between the actions of optical antipodes upon them might be explained by supposing that the asymmetric nerve substance combines more readily with one antipode than with the other. This, however, is pure theory.

The sense of sight is the last one with which we can deal. Byk[7] has shown that a solution of potassium copper racemate differs in tint from a solution of the potassium copper salt of dextro tartaric acid. Thus, the only sense which is not yet proved to be affected by optical isomerism is that of hearing. Even this might conceivably be influenced by differences in the rate of transmission of sound in active and racemic substances; but, so far, no experiments have been made in this direction.

We must now turn to another branch of the subject, and consider those cases in which isomerism is due to the presence in the molecule of a double bond between two atoms. The Le Bel-van't Hoff hypothesis assumed that, in the case of a single bond between two carbon atoms, free rotation of the atoms about their common axis was possible; but when we come to a compound containing a double bond, this postulate is abandoned, and it is assumed instead that the double linking of the atoms introduces an element of rigidity into the molecule. We may retain the tetrahedral symbols in this case also, and represent the compound ethylene, $CH_2:CH_2$, by two tetrahedra laid edge to edge instead of apex to apex, as in the previous cases.

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[1] Fischer and Hagenbach, *Ber.*, **34**, 3764 (1901).

[2] Menozzi and Appiani, *Atti R. Accad. Lincei* [5], **2**, II. 421 (1893).

[3] van Ekenstein, *Rec. trav. chim.*, **15**, 222 (1896).

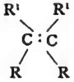
[4] Neuberg and Mayer, *Zeit. physiol. Chem.*, **37**, 545 (1903).

[5] Sternberg, *Archiv Anat. u. Phys.*, **1898**, 457.

[6] Marckwald and McKenzie, *Ber.*, **32**, 2130 (1899).

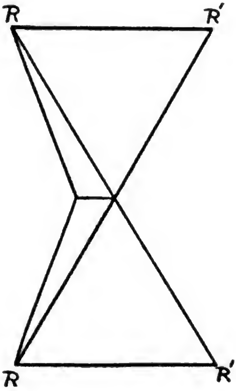
[7] Byk, *Zeit. physikal. Chem.*, **59**, 682 (1904).

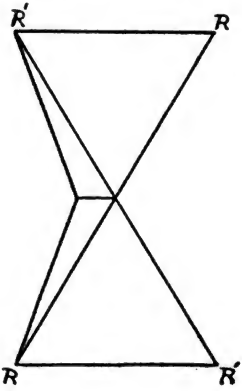
When we substitute other atoms or radicles for the four hydrogen atoms, we shall find that under certain conditions we have a system which is capable of two space arrangements. The necessary conditions are simple: we need only ensure that the two groups attached to each carbon atom differ from one another. In other words, isomerism is to be expected in its simplest form in the case of an ethylene derivative.



$$\begin{matrix} R' & & R' \\ & C:C & \\ R & & R \end{matrix}$$

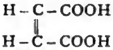
The two possible special arrangements are those represented by:





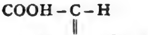
In the first case the two groups R lie one above the other, while in the second figure R lies over R^1; and since free rotation of the carbon atoms is assumed to be precluded by the nature of the double bond, no change in configuration can take place under ordinary conditions. It should be noted that all four groups $RRR^1 R^1$ lie in one plane, so that no isomerism due to enantiomorphous arrangements of atoms is to be expected, nor have these isomers any action upon the plane of polarisation. To distinguish these isomers from those containing asymmetric carbon atoms it is usual to term them *geometrical* isomers, as distinct from optical isomers.

The best known case of geometrical isomerism is that of maleic and fumaric acids, which may be represented thus, if the tetrahedra be omitted:



$$\begin{array}{c} H-C-COOH \\ \| \\ H-C-COOH \end{array}$$

Maleic Acid



$$\begin{array}{c} COOH-C-H \\ \| \\ H-C-COOH \end{array}$$

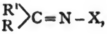
Fumaric Acid

When maleic acid is heated above its melting-point it is converted into fumaric acid. The former body is therefore termed the *labile* form, while fumaric acid is known as the *stable* isomer. As in the case of optical isomers, we may give here a table showing the principal physical properties of maleic and fumaric acids:

	Maleic Acid	Fumaric Acid
Melting-point	130°	Sublimes unchanged
Affinity Constant	1·17	0·093
Specific Gravity	1·590	1·625
Solubility in water	1:2	1:150

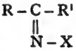
An extension of the hypothesis of geometrical isomerism to nitrogen compounds was made in 1890 by Hantzsch and Werner.[1] They assumed that when a carbon atom is doubly linked to a nitrogen atom, the third valency of the nitrogen atom is directed at a certain angle to the other two.

Now, in the compound

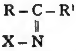


$$\begin{matrix} R^1 \\ R \end{matrix}\!\!>C=N-X,$$

it is obvious that X may be supposed to lie near R or R^1; so that in this case also we have the possibility of two geometrical isomers:



$$\begin{array}{c} R-C-R^1 \\ \| \\ N-X \end{array}$$



$$\begin{array}{c} R-C-R^1 \\ \| \\ X-N \end{array}$$

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[1] Hantzsch and Werner, *Ber.*, **23**, 11 (1890).

Much less attention has been given to the physiological action of stereoisomers of this type; and when we examine the literature of the subject, only a few scattered references are to be found. The cause of this apparent neglect is to be found in the fact that many of the alkaloids used in medicine occur in optically active forms, while geometrically isomeric bodies find no considerable place in pharmacology.

We may consider in the first place the effect which this type of isomerism exerts upon fungi. The fungus *Penicillium glaucum* grows readily in fumaric acid solution, but does not thrive in a solution of maleic acid. Using *Lupinus albus*, *L.*, Kahlenberg and True[1] established the following figures. When the fungus was introduced into a solution containing 116 grammes of acid in 6,400 litres of water, it died. When the solution was diluted to twice its volume, the organisms were able to live in the weakened solution. 116 grammes of maleic acid dissolved in 3,200 litres of water produced a solution incapable of supporting the organisms; but on dilution to 6,400 litres it became fit to support the fungi. These two sets of results, pointing as they do in opposite ways, seem to indicate a difference in the configurations of the active tissues of fungi, *Penicillium glaucum* being capable of attacking fumaric acid, *Lupinus albus*, *L.*, has a greater power of breaking down maleic acid. Further research in this field might lead to very interesting results, as the case seems to form a parallel to the action of ferments upon sugars, with which we have already dealt.

In toxic action the two acids differ considerably, as Ishizuka[2] has proved. In his experiments he took 1·94 grammes of acid for each kilogramme of dog used. This, in the case of maleic acid, proved a fatal dose; while with fumaric acid the same dose had no effect. It should be noted, however, that this result may be due to a difference in the strength of the two acids, maleic acid being much stronger than fumaric.

Toxic action, however, is not the only property in which these isomers show differences. It has been found that in the case of the compound benzyl-β-amidocrotonic ester, whose two configurations are shown below, the one form (M.P. 79°) is tasteless, while its isomer (M.P. 21°) has an intensely sweet taste, which resembles that of peppermint. The two configurations are shown below:

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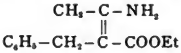
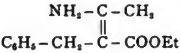
[1] Kahlenberg and True, *Botanical Gazette*, Chicago, **22**, 181 (1896).

[2] Ishizuka, *Bull. Coll. Agr.*, Tokyo, **2**, 484 (1897).

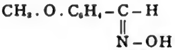


$$\begin{array}{r}CH_3-C-NH_2\\ \|\quad\quad\\ C_6H_5-CH_2-C-COOEt\end{array}$$



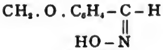
$$\begin{array}{r}NH_2-C-CH_3\\ \|\quad\quad\\ C_6H_5-CH_2-C-COOEt\end{array}$$

A similar example is found in the case of the aldoximes: the syn-form of anisaldoxime is tasteless, while the anti-form is very sweet:



$$\begin{array}{r}CH_3.O.C_6H_4-C-H\\ \|\quad\\ N-OH\end{array}$$

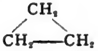
Syn-form



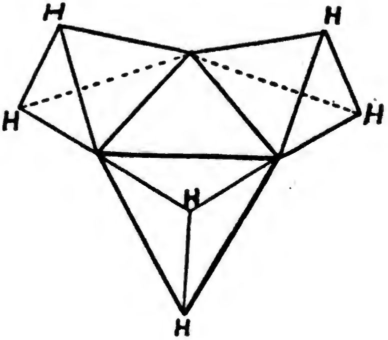
$$\begin{array}{r}CH_3.O.C_6H_4-C-H\\ \|\quad\\ HO-N\quad\end{array}$$

Anti-form

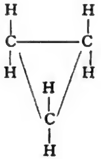
We must next deal with another case in which the rotation of carbon atoms about their axis of junction is hindered. When three or more carbon atoms are joined together to form a cyclic compound like trimethylene:



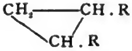
there are two important consequences. In the first place, free rotation of the carbon atoms becomes difficult, if not impossible. This can be seen by building up a model, when it will be found that a disruption of the molecule would almost certainly result from any such rearrangement. Secondly, the six hydrogen atoms in trimethylene are arranged in two parallel planes, the carbon atoms lying in a third plane between these two and parallel to them.



To save space in printing, this is usually written in the following way:

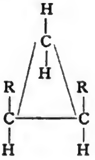


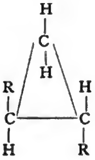
Now, here, as in the case we have already dealt with, substitution may produce a difference in configuration; for if we take the case of the compound:



we shall find that there are two possible spacial arrangements of the atoms. In the first, we have the two groups R and one hydrogen atom in the same plane, while in the second arrangement we have one R group and two hydrogen atoms in the same plane:

(I)

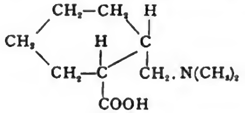




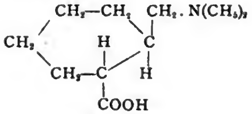
(II)

Form (I) is called the *cis*-form; form (II) the *trans*-form.

In this section two instances are known in which the two isomers differ from one another in smell. In each case the cis-form has a stupefying odour, while the trans-isomer is devoid of smell. The substances in question are the hexahydro-*o*-diethyl-benzylamine carboxylic acids:

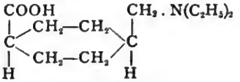


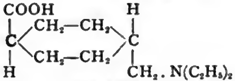
Cis-form



Trans-form

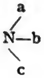
and the hexahydro-*p*-diethyl-benzylamine carboxylic acids:


Cis-form


Trans-form

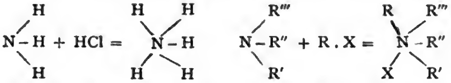
In the foregoing paragraphs we have been concerned with compounds which owed their isomerism to some peculiarity either in the arrangement of radicles round a carbon atom, or in the mode of linkage between atoms. We must now turn to the question of an isomerism which is due to other types of asymmetry, and we may commence with the case of asymmetric nitrogen.

Without going into any intricate details, it may be said that when a nitrogen atom is united to three separate radicles, no isomerism is to be found. Of course, as has been mentioned already, a nitrogen atom doubly linked to a carbon atom may give rise to isomerism, but in the case of a compound such as:



no isomerism occurs; and it is therefore assumed that the groups *a*, *b*, and *c* and the nitrogen atom lie in one plane or are free to move about in space. Were this not so, we should expect to find enantiomorphism shown by such substances.

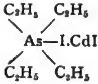
When we allow a tertiary amine to react with an alkyl halide, a quaternary ammonium salt is formed, just as ammonia and hydrochloric acid unite to form ammonium chloride:



When the four alkyl groups attached to the nitrogen atom differ from each other, as in the case of NRR′R″R‴Cl, the nitrogen atom is asymmetric, and the compound is found to exist in two enantiomorphous forms of equal and opposite rotatory power. The case is parallel to that of the asymmetric carbon atom. It is evident that in passing from the trivalent to the pentavalent condition of the nitrogen atom we have passed from a plane configuration of the molecule to one of three dimensions.

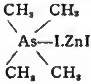
Crum Brown and Fraser[1] have shown that when certain alkaloids containing a trivalent nitrogen atom were allowed to unite with methyl iodide, they gained a new physiological property without losing any of their previous efficiency. The new attribute which they acquire by this increase in the valency of their nitrogen atoms resembles the chief property of curare, for these new methyl iodide addition products have a paralysing action upon the ends of the motor nerves of muscles. Curare itself contains a tertiary base curine, and Boehm[2] has shown that when curine is treated with methyl iodide it yields the quaternary salt curarine, which is two hundred and twenty-six times as poisonous as the mother substance, and which possesses in an acute degree the paralysing properties of curare. The most probable deduction from these results is that the change in the valency of the nitrogen atom lies at the root of these effects; but we must inquire further whether the consequent change in configuration has not some bearing upon the point.

Fortunately, the evidence on this subject is already at our disposal. We need only replace the nitrogen atom by some other atom which has the same faculty of changing from the trivalent to the pentavalent condition; and we are not hampered in our choice in this matter, as no fewer than three other elements have been examined by Vulpian.[3] The substances actually used by him were: (i) tetra-ethyl-arsonium cadmium iodide, (ii) tetra-methyl-arsonium cadmium iodide, (iii) methyl-triethyl-stibonium hydroxide, and (iv) tetra-ethyl-phosphonium iodide:



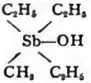
$$\begin{matrix} C_2H_5 & & C_2H_5 \\ & As{-}I.CdI_2 & \\ C_2H_5 & & C_2H_5 \end{matrix}$$

(i)



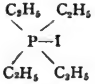
$$\begin{matrix} CH_3 & & CH_3 \\ & As{-}I.ZnI_2 & \\ CH_3 & & CH_3 \end{matrix}$$

(ii)



$$\begin{matrix} C_2H_5 & & C_2H_5 \\ & Sb{-}OH & \\ CH_3 & & C_2H_5 \end{matrix}$$

(iii)



$$\begin{matrix} C_2H_5 & & C_2H_5 \\ & P{-}I & \\ C_2H_5 & & C_2H_5 \end{matrix}$$

(iv)

None of these substances shows the ordinary physiological behaviour of arsenic, antimony, or phosphorus, but all of them have a strong curare-like action, which seems to indicate that that action is due rather to the molecule as a whole than to the nature of the atom at the centre of the complex.

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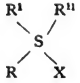
[1] Crum Brown and Fraser, *Trans. Roy. Soc. Edin.*, **25**, 707 (1868); *Proc. Roy. Soc. Edin.*, **1869**, 560.

[2] Boehm, *Archiv de Pharmacie*, **235**, 660 (1897); *Archiv exp. Path. u. Pharmak.* **6**, 101.

[3] Vulpian, *Archiv de phys. norm. et pathol.*, **1**, 472; see also Bürgi, *Archiv. exp. Path. u. Pharmak.*, **56**, 101.

Another example of the change of a plane molecular configuration into a three-dimensional one is to be found in the case of the sulphur compounds. In the alkyl sulphides having the formula $R - S - R'$, since there are only three groups, the configuration must be a plane one. When alkyl iodides are added to these sulphides, however, optically active substances can be produced, having the formula:



and from the occurrence of optical activity it is supposed that this case is analogous to that of the asymmetric carbon atom; and that the radicles R, R′, R″, and X are arranged at the corners of a tetrahedron whose centre is occupied by the sulphur atom. Of course this tetrahedral arrangement will persist even if the sulphur atom be not asymmetric and no optical activity is shown. Now Curci and Kunkel[1] have found that sulphine bases, such as trimethyl-sulphine hydroxide $(CH_3)_3 . S . OH$, have a pronounced curare-like action, which is lacking in the sulphides.

Similar results have been obtained by Bock[2] in his study of the ammonia derivatives of cobalt, chromium, and rhodium, which resemble each other to a certain extent. He was able to show that the nature of the metallic atom in the molecule had less influence upon the physiological action than was exerted by the general character of the compound.

Since in all these cases a change from a plane configuration to a three-dimensional one is taking place, and since, previously, we have shown how great an influence upon the physiological action of certain substances is exerted by a difference in the spacial arrangement of their atoms, we are not unjustified in assuming that the change in configuration has some influence in this case also.

Stereochemistry is usually divided into two sections. In the one division we deal with the purely static (or at least hypothetically static) relations between atoms which give rise to isomerism; in the second section we are concerned chiefly with the dynamic effects of certain atomic groupings, their influence upon chemical reactions, and similar subjects. In the foregoing pages we have restricted our examination to the first division, and have dealt purely with the question of stereo-isomerism and its connection with the action of certain substances upon living tissues; but we must now turn to the second part of the subject and discuss the dynamic influence which certain atomic groups may exert upon others.

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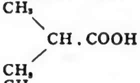
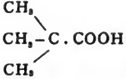
[1] Curci, *Archiv de pharm. et de therap.*, **4**, 1896; Kunkel, *Lehrbuch der Toxikologie* (1901).

[2] Bock, *Archiv exp. Path. u. Pharmak.*, **52**, 1, 30 (1904).

When we allow acetic acid to react with ethyl alcohol in presence of hydrochloric acid, water is eliminated and ethyl acetate is formed:

$$CH_3.COOH + C_2H_5OH = CH_3.COOC_2H_5 + H_2O$$

Now, the researches of Menschutkin, Sudborough, and Lloyd, and others[1] have shown that when substituted acetic acids are used instead of the parent substance, the amount of ester formed under given conditions decreases. The amount of this decrease depends on the complexity of the acid, and is quite independent of its strength, as the following table shows:

Formula of Acid.	Amount of Ester.	Affinity Constant.
$CH_3.COOH$	3·661	0·00180
$CH_3.CH_2.COOH$	3·044	0·00134
 $(CH_3)_2CH.COOH$	1·0196	0·00144
 $(CH_3)_3C.COOH$	0·0909	0.000978

A similar decrease in the amount of ester formed is found if the complexity of the alcohol be increased while the acid remains the same throughout, *e.g.* when acetic acid is esterified with methyl, ethyl, isopropyl, and tertiary butyl alcohols. It is evident, therefore, that the cause of the decrease in the amount of ester formed is to be sought in the change in structure of the acid or of the alcohol. On examining the formulæ shown in the table, we find that in each case as we go down the table we are replacing a hydrogen atom by a methyl radicle. In other words, we are exchanging a small light group for a large heavy one.

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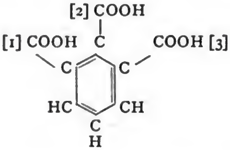
[1] Menschutkin, *Ann. chim. phys.* [5], **20**, 229 (1880); **23**, 14 (1881); **30**, 81 (883); *Journ. Russ. Phys. Chem. Soc.* **9**, 316, 346 (1877); **10**, 278 (1878); **11**, 24, 345 (1879); **12**, 82 (1880); **13**, 564 (1881); **16**, 356 (1884); *Ber.* **13**, 1812 (1880); **30**, 278 1897); *Annalen der Chem.*, **195**, 334 (1879); **197**, 193 (1879); *Journ. Chem. Soc.*, **8** , 1532 (1906); Sudborough and Lloyd, *ibid.* **75**, 467 (1899).

Let us next consider what takes place when an acid reacts with an alcohol. Obviously the hydroxyl group of the alcohol must come within range of the carboxyl group of the acid before any interaction can take place, since the ester is formed by the elimination of water between these two groups. Now, if we could interpose some barrier between these two radicles, we should hinder the esterification; and the more effective the barrier was, the less ester would be formed. Such a barrier is found in the methyl groups of the substituted acetic acids. According to the current theories of chemical action, a certain amount of free space must exist around the hydroxyl group before the carboxyl radicle can come within reaction range. The light hydrogen atoms are easily thrust aside by the heavy carboxyl group, and therefore the esterification of acetic acid is easy. When we replace the light hydrogen atoms by the heavier methyl radicles, however, the resistance to the entrance of the carboxyl radicle becomes serious, and consequently much less ester results. The following analogy may help to make the matter clearer: Suppose a man to be desirous of passing through a certain door, guarded by children. He would be able to pass because his strength would be greater than that of the guards; but if the children became men, his chances of passing the door would be very considerably reduced.

This *steric hindrance*, as it is called, has been observed in nearly every class of reaction; and there seems to be no doubt that the substitution of one group for another may influence the course of a reaction to an extent which seems quite out of comparison with the slight change in the chemical character of the substance which the substitution produces. We must now consider an application of this view to the question of vital action.

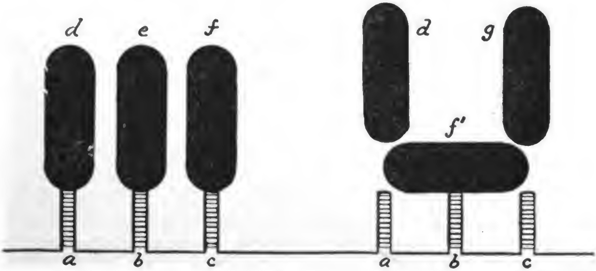
On Ehrlich's theory of antitoxins there are two sets of molecules in living tissue: those on the outer surface of the cells being concerned with the nutrition process, while those within are employed in cell metabolism. If the outer, or peripheral, molecules can be put out of action, the cell lacks nutrition and eventually dies. Ehrlich supposes that the peripheral molecules have active side-chains serving to anchor suitable molecules which may be carried past them; and in this way the cell extracts the necessary nutriment from bodies carried past it in the blood currents. These side-chains, however, may serve to anchor toxin groups as well as nutritive ones; and, on Ehrlich's view, when a sufficient number of toxin groups have been anchored, the nutrition of the cell may suffer to such an extent that the cell dies.

Schryver[1] has put forward a different view of what takes place. A concrete example will make the matter clearer, and for the sake of simplicity we may symbolise the cell by the benzene tricarboxylic acid shown below:



Here the active side-chains are represented by three carboxyl radicles. Now suppose that a molecule of aniline passes within the range of the central carboxyl group (2), and is seized and anchored by it. The presence of this large group will hinder the approach of other aniline molecules to the carboxyl groups (1) and (3), so that they will be temporarily put out of action until the first aniline radicle is disposed of.

We may represent the action diagrammatically in the following way:



(a) FIG. 1. (b)

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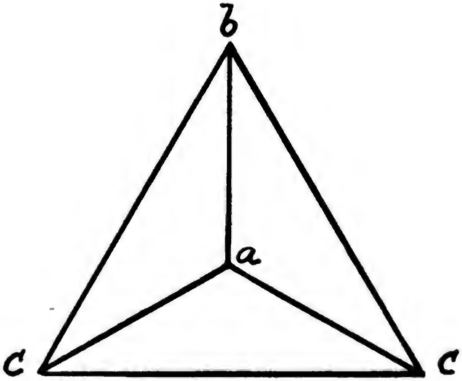
[1] Schryver, *Chemistry of the Albumens*, p. 183 (1906).

In fig. 1*a* the side-chains are represented by the unshaded parts *a*, *b*, and *c*, while the molecules of nutritious substance are represented by *d*, *f*, and *g*. It is obvious that the presence of the molecule *f* on *b* will not interfere to any extent with the action of *a* or *c*. This symbolises the normal action of the side-chains. If, however, the central side-chain *b* should happen to anchor the abnormally large body f^1 (fig. 1 *b*), the state of affairs would be quite different; for f^1 occupies so much room that the side-chains *a* and *c* could not come into play, and the cell would consequently be starved. On Schryver's view, then, toxicity in a tissue may be regarded as due to a steric hindering of normal functions.

Before concluding this article, some mention should be made of the relation between vital action and the production of molecular asymmetry. When in the laboratory we convert a compound $Cabc_2$ into another, *Cabcd*, which contains an asymmetric carbon atom, it might be expected that an optically active product would result. In practice, however, this does not occur; for instead of one antipode being produced, the final product is racemic. A consideration of what takes place in the course of the change from $Cabc_2$ to *Cabcd* will make clear the reason for this. In the substance $Cabc_2$, we are dealing with a tetrahedral arrangement of atoms like that shown below:



The two groups *c* are identical. Now, if the right-hand *c* be replaced by *d* we shall have one compound, while if the left-hand *c* be chosen for replacement we shall have the optical antipode. Since the optical antipodes are identical in chemical properties and differ physically only in respect to their crystalline forms, there is no reason why the dextro form should be formed rather than the lævo form; and there is no reason why one *c* should be replaced rather than the other, since they are symmetrically situated with regard to one another. It is, therefore, only natural that in one half of the total number of molecules the right-hand *c* is replaced by *d*, while in the others the left-hand *c* is chosen, the result being a mixture of the two antipodes in equimolecular proportions.

We may take it as a general rule, then, that from symmetrical substances only symmetrical products are formed in the course of our laboratory reactions. On the other hand, when we examine the constituents of living tissues we find that a very large proportion of them are optically active substances, so that at the first glance there appears to be a profound difference between chemical actions in the laboratory and those which are carried out within living organisms. At present those chemists who take an interest in the matter are divided into two schools. The one school holds that there is no fundamental difference between the chemical processes of vital action and the chemical processes of the laboratory; while the other school maintains that the question of molecular asymmetry sharply divides the two sets of phenomena. Up to a few years ago, neither view could call any experimental evidence to its assistance. The case of sodium ammonium racemate was cited by the "uniform" school as a proof of their case. This substance, if allowed to crystallise from its solution under certain conditions of temperature, separates spontaneously into two sets of crystals which, owing to the difference in the disposition of their hemihedral faces, can be separated by hand from each other. The upholders of the vitalistic theory of molecular asymmetry, however, pointed out that in order to separate the two vital action was necessary, since a human being was a vital agent. It is unnecessary here to enter into the details of the arguments employed on both sides; they are to be found in the correspondence in *Nature*,[1] and were chiefly theoretical.

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[1] *Nature*, vols. 58 and 59 (1898-9).

The question appears to have been settled in a somewhat unexpected manner. Cotton,[1] examining the absorption of dextro circularly polarised light by copper ammonium tartrate, found that the two tartrates did not possess identical powers of absorption. Now, if light is absorbed by any molecule, some extremely delicate rearrangement of the molecule's internal structure must take place; for we cannot imagine that a vibration can be stopped without some energy being expended in stopping it or changing its amplitude. Therefore, in the case of the dextro and lævo forms of copper ammonium tartrate, more energy is being used up by the one form than by the other; and hence the intramolecular readjustment is greater in the one isomer than in the other. In other words, dextro circularly polarised light is an agent which favours one form of tartaric acid rather than the other. Now, Byk[2] has pointed out that light is circularly polarised by the surface of the sea, and that one variety of the circularly polarised light predominates on the earth's surface. This obviously furnishes us with an asymmetric agent whose application, as far as the earth is concerned, is nearly universal; and it seems not improbable that some such cause, acting under favourable conditions, may have given rise to a preponderance of a right-handed or left-handed form at one particular period in geological history. Until some active substance is actually synthesised by this method, however, the question must be regarded as, at least technically, an open one.

It should be noted that once the presence of an asymmetric substance is granted, the subsequent steps up to the present complex series of naturally occurring asymmetric forms become simple to understand. A very small quantity of an asymmetric acid, under suitable conditions, may serve to resolve any quantity of a racemic base without losing any of its peculiar asymmetry; while each portion of base resolved into its antipodes becomes a new centre for the resolution of racemic acids, which in their turn may serve to resolve new bases, and so on *ad infinitum*. The case is analogous to that of ordinary animal reproduction, since with each generation the reproductive power increases in geometrical proportion.

In conclusion, it may be pointed out that the accumulation of further data as to the action of stereo-isomers upon animal tissues is very desirable. Since a slight difference in structure may produce a great difference in the action of drugs, it seems advisable to begin by investigating those cases in which the structures of the bodies are identical, and the only difference lies in the special arrangement of the atoms. At the present time the data in this branch of the subject are only sufficient to show that the influence of stereo-isomerism is of importance; they are not full enough to enable us to draw any general conclusions.

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[1] Cotton, *Ann. chim. phys.* [7], **8**, 373 (1896).

[2] Byk, *Zeit. physikal. Chem.* **49**, 641 (1904); *Ber.* **37**, 4696 (1904).

THE PROPAGATION OF PHYSIOLOGICAL CHANGE

A PHYSICAL PROCESS

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It is a leading characteristic of living matter that it is readily excited by slight sudden changes in its environment. To these stimuli it frequently responds by chemical and physical reactions in which much more energy is transformed than was supplied by the exciting cause, in this way resembling all unstable structures and compounds. It differs, however, from these unstable bodies in that it rapidly returns to its original state, abstracting matter and energy from its surroundings to make good its loss—a process which can be repeated indefinitely. Nor is the word indefinitely made use of in any limited sense, as will be apparent when the processes of growth and multiplication are considered. Unstable when momentary changes are dealt with, stable when time is taken in larger units, living matter is usually spoken of as "labile."

Now when an attempt is made to penetrate the meaning of this state there are certain facts which always obtain a primary hearing for circumstances of purely chemical rank. In the first place many of these exciting causes lead obviously to chemical change, as in the case of muscle, from which, when excited, waste products trail away as definitely as the smoke and fumes from any chemical factory. In the second place there is no doubt that all the energy transformed in the body is liberated as a consequence of the oxidation processes by which its food material is overtaken. This statement has within recent years been placed in a position of almost absolute truth.

Explanations of both phases of this condition of lability have therefore most frequently been arranged in terms of chemical reactions. At one time we were invited to think of these vaguely as due to processes of assimilation and dissimilation, anabolism and katabolism; no very certain limit being placed to the meaning of these terms. Alongside of the processes leading to the formation of an unstable and highly complex product were also processes leading to its destruction, and both sets of processes were characteristic of the normal resting state of living matter. Stimulation led to a new quantitative relation between the two, so that momentarily the destructive process was dominant. During the recuperative period following excitement the constructive process was dominant in its turn.

More recently considerations introduced by Ehrlich, as also the time relations of the oxidation process observed by Hermann, have served to modify and harden this view. It is on the one hand made clear that the destructive process need not be postulated as overtaking more than a certain fraction of the molecule, or, as it is expressed, no more than certain of its side chains. On the other hand also the constructive process can be imagined as repeatedly recommencing from a constantly surviving level of considerable perfection. Verworn has therefore brought to our notice a certain stable atom-complex, or nuclear group, to which more unstable side chains are linked under pressure of ordinary chemical and physical circumstance. In these and between these side chains perpetual change occurs, which is exaggerated and perhaps given a new direction by the incidence of stimulation. Every act of "life" therefore has its basis in the chemical changes taking place on the fringe and within the influence of these residual nuclear molecules. This at least if certain "enzymes" are allowed to play a part less definitely assessed, and take a place in the molecule less definitely assigned.

To satisfy the intimacy of intracellular life the conception has been tentatively extended by a hypothesis first boldly introduced by Pfluger. The residual atom-complexes are linked together to form a giant nuclear molecule which occupies a great share of the space within the cell, as for example the whole of that process of a nerve-cell known as the core of a nerve-fibre. In this way we have in front of us a schema which clearly illustrates the conception that "life" is primarily dependent upon chemical structure, and that all the expressions of life are the outcome of chemical change. This conception has indeed been welcomed as serving usefully to link together many experimental facts. In the first place those facts upon which it was based, the storage of oxygen within the cell in chemical combination alongside of oxidisable material to which it is finally handed over. In the second place such instances as those in which minute traces of specific chemical materials modify the life and activities of the cell. In this latter case the concept has justified its existence by indicating fruitful lines of experiment. Its influence has also been clearly felt in further elucidating the importance of oxygen not only to life, but also to function.

We must ask, however, whether no position of importance should be accorded to states and changes of a purely physical kind. Surely these also play their part within the cell. Their influence upon extra-cellular material is often paramount, and it is perhaps best by a consideration of this influence that their case may be introduced. Let us for example consider a rod of cartilage. Here cells are situated in a mass of tough material which they have manufactured. Unlike their epithelial cousins situated on the surface of the body, they do not pass their manufactured products on to a surface from which in the course of events these are swept away. The cells are therefore separated by a greater amount of material, which first oozing from them as a viscid mass no more rigid than its source, then sets into the tough elastic substance to which the cartilage owes its physical characteristics and its sole use. Now who can deny the probability that this process of "setting" is due to stimulation provided by the stresses and strains to which the exuded material is at once subjected? We thus get a picture of this extracellular material undergoing a change of physical state of functional importance, and that as the result of excitation. Again, as the cartilage plays a frequently repeated part in the stresses and strains to which the limb is subjected by muscular action and external pressure, certain points within it are selected as the foci through which resultant forces pass. These most probably are the "centres of ossification." The forces in action arrange the cells and matrix in columns radiating from this centre. The stimulated matrix continues with its change of state, the colloid material passes from the condition of a homogeneous jelly into one in which there is a precipitation of denser "calcified" material from a more simple solution readily removed; condensation and liquefaction. Is this a chemical change resulting from the exudation of a new corrosive substance from the excited cells, or is it a physical consequence of repeated pressure upon the homogeneous jelly? It is clear that the mass primarily stimulated is the jelly, which from its consistence must be held to protect the cells enclosed within it. Again, the irruption of bone-forming cells takes place, made possible by the liquefactive change. Each one of these new cells secretes an exudate which then "sets." The directions taken by the fibres precipitated in the setting bone-matrix at once suggest the notion that they are the result of the stresses and strains to which the material is subjected. Calcium salts also make their appearance passing from a state of solution to be precipitated as granules. In the case, then, of bone-formation it is again the change of physical state which at once claims our interest. Now it may be objected that there is no proof that these changes are not of chemical rank, perhaps even attended with an output of waste products. However, even if that possibility be admitted, the contrary hypothesis is seen to be at least as admissible, and therefore to require definite examination.

But if a case can be made out for the examination of such possibilities when dealing with extracellular material, the same possibility must also be introduced within the limits of the cell. The difference between similar changes within and without the cell may be no more than a difference of opportunity and advantage. Outside the cell the sole sources of energy are those provided by stimulation and the heat of the circulating solutions of the body. The cell has the advantage here. Inside the cell recovery may thus be more usual than outside of it. Within the cell, as for example in the musculature, is the source of heat production whence the heat of these circulating solutions is derived. Within the muscle-fibre itself this chemical source of energy may play no greater part in many important internal processes than is played by the heat of the forge in the production of steel. If the muscle distributes heat to other tissues of the body which is made use of in this way, what limits are to be set to its own participation in similar advantages? It is a possibility often lost sight of, but none the less important, that the source of energy within the muscle may possibly be responsible for physical states, *for physical stores of potential energy*, the disturbance of which in their turn may give rise to a development of heat. Heat so produced is to be traced finally to the combustion of food material as surely as that directly produced by the occurrence of concomitant chemical change.

So far I have done no more than consider the possibility that physical state and change may be of importance in intracellular change. Let us consider a case where they must of necessity be introduced—as for example in the secretion of water as sweat at a point upon the surface of the skin. Below this surface there extends a long tubular pocket lined by epithelial cells. These cells are suddenly aroused from a state of rest by the arrival of a nervous impulse dispatched from the central nervous system; after a short delay water wells from the mouth of the pocket on to the skin. Whence does this water come? Certainly not from the side links of any "biogen molecule" within the cell. The water has indubitably been drawn through the cell from the solutions bathing its internal surface. The cell has acted as a pump in which valves give a direction to the work performed. Now how is this to be dealt with if the physical arrangements of the materials forming the cell are not to be placed in the foreground as matters of importance? Discuss these arrangements and it at least becomes possible to conceive a line of experimental approach to the phenomenon.

Let us for a moment suppose that, as is most probable, the internal and external surfaces have characters of a different kind. In some epithelial cells such differences can be seen. In all, even including the nerve-cell, such differences must be inferred. Let us suppose that this cell, set upon the surface of the body, is in the habit of passing some of its waste products, as for example carbonic acid, not back into the solutions of the body, but out on to its external surface. What more probable? But then, if so, we have only to imagine that our exciting nervous impulse quickens up the chemical changes occurring within the cell and so gives rise to the production of carbonic acid. These new molecules, added to the physical value of the cell as a mass of molecules in a state of solution, are the cause of an increased osmotic pressure which is sufficient with the differences postulated between the cell surfaces to account for the passage of water out into the pocket of the little gland. Here we have been forced to think of the matter within the cell as a solution, of a chemical change as merely adding to the number of molecules in solution, of the cell limits as permitting or restraining the motion of dissolved material. None of the important activities underlying these terms are made obvious by the contemplation of "biogen molecules."

Let us examine an instance a grade more complex. The salivary glands are formed of similar pockets, from which on the arrival of a nervous impulse water again gushes out on to the surface of the body containing in solution organic and inorganic matter. The same explanation will temporarily cover the output of water. But why these other substances also? Now there is no doubt that most of these other materials have lain within the cell long before the arrival of the nervous impulse, having been manufactured during hours of rest from secretion. They are now merely washed out in the rush of water. In addition to the chemical work done on receipt of the impulse we have here to consider specialised chemical work performed quite independently of this, such as is done by gland-cells to which no such impulses come. Is it of advantage to consider the molecules engaged in the one change and in the other as necessarily the same? Is it not simpler to think of molecules of diverse kinds in solution side by side but undergoing a different cycle of change with intensities that reach their maxima at different times? We have been compelled to introduce the concept "solution" to explain the transit of water. There can be no doubt now, as the result of manifold experiment, that this concept has to be introduced in case of every cell; nor even any doubt, to make the matter physically more complex, that the variations of phase within these solutions undergoing change with every kind of alterations in physical circumstance have all to be taken into consideration as modifying the activities of the cell, and therefore as variable physical states of functional importance.

Now it may be said that, after all, these instances have done no more than attribute important results to chemical change as the primary source of energy directly involved in the processes considered. The carbonic acid production has been dealt with as the source of the change. But what if we select as our new molecule adding to osmotic pressure not carbonic acid, so obviously the outcome of an oxidation process, but some inorganic salt? In the case of the salivary secretion certain experimental facts render a consideration of this possibility necessary. Here the chemical side is not so obvious, since we may suppose these molecules to have been pre-existent within the cell, and to be liberated not from a position of chemical combination, but from some position of physical restraint on arrival of the nervous impulse. This is a possibility with an important distinction. The whole sudden energising of the cell is made to take an entirely physical form. In this case, however, the chemical side must not be lost sight of. We must suppose that, during its rest from secretion, the chemical energy of the cells was utilised in producing this physical condition of restraint, and so feeding a secondary source of energy conveniently available at the moment of stimulation.

And now, having prepared the way by means of allegory, I would turn to the specific instance which I am more concerned in protecting from this purely chemical conception of function. If living material is at one time stable and unstable, is labile, where is this fact more obvious than in the case of nerve? Excited by almost every slight change of environment to a display of function and therefore most unstable, but recovering so rapidly that within one five-hundredth of a second it can be provoked to an exactly similar change of state—a process which under favourable conditions can be repeated from dawn to dewy eve without giving rise to any trace of fatigue. Pancreas cells may be unexcited to their specific function save on the addition of certain specific chemical materials. Mammary-gland cells may preserve a similar scorn for fleeting change. In them obvious chemical work is done, and the chemical composition of the media in which they lie is their main concern, of which they are not oblivious; but of their extreme lability what proof have we? Astonishing pictures of exhausted cells indeed form evidence for an opposition. Turn to nerve-fibres and the facts are curiously reversed. Most stable and yet most unstable, "labilissimi," what proof have we of the primary importance of their chemical constitution and its changes? Practically none. I shall escape impeachment for this statement. The main fact is so clear notwithstanding some slight evidence to the contrary. Thus Waller has in most ingenious fashion shown that prolonged stimulation leads to just such a modification of conduction as is producible by carbonic acid, but not unproducible by other factors also. Bethe has shown that prolonged stimulation is followed by an alteration in staining capacity with certain basic dyes, a circumstance which may have no more meaning than an alteration in physical state. It is true that this absence of chemical evidence may be ascribed to the minute quantity of change involved, and to the swift flight of the nervous impulse.

It is no doubt true that the maintenance of life in the nerve-fibre is dependent upon chemical factors. As is the case with all intracellular material, the continuance of its function is ultimately dependent upon a complex of chemical and physical states to which the cell-nucleus, nutriment, oxygen, and the removal of waste products such as carbonic acid are essential. Doubtless, too, this complex is affected by narcotics in some cases, in a manner to be assigned to the inhibition of certain essential chemical processes. No doubt also drastic interference with this complex may produce an abnormal physico-chemical state in which symptoms of fatigue become obvious, as in the instance of the effects of aconitine observed by Waller, chloroform by Garten, lack of oxygen by Frohlich. But here we have our fingers upon the very acme of lability. This is the tissue from which many of the conceptions of lability of living matter are derived. It is significant that here of all places we should have to hunt so desperately for instances of chemical change. There is, then, excellent reason why, on a basis of experimental fact, nerve should not be used in illustration of the value of any purely chemical concept of function.

Thus that rapid propagation of physiological change from point to point which is the leading function of nerve, but is by no means confined to nerve, is doubtless always due to the conveyance of a physical change. The train of gunpowder is apparently a simile to the contrary, but I believe I am right in insisting that in this case the explosion of each segment in turn is due to a rise in temperature. That physical factors are alone responsible for the similar excitation of each successive piece of nerve has been laboriously proved by a study of the action of every admissible form of stimulus. Efficient physical forms of stimulation are, the incidence of light, a rise of temperature, a slight mechanical shock, pressure, a sudden fall of electrical potential, sometimes a fall of temperature, sometimes a rise of electrical potential, sometimes the removal of pressure. Every sudden change in physical environment is liable to stimulate nerve. Efficient chemical means are all illusory. Only such chemical reagents as have a capacity for indirectly producing physical change are capable of stimulating. Their effects are then in proportion to the physical change which they are capable of producing, as has been well shown by Matthews. Solutions of electrolytes produce electrical effects. Solutions of varied concentration cause variations in the water content of the nerve. Concentrated solutions by concentrating the electrolytes in the interior of the nerve give rise to self-stimulation. The transference of the excited state from point to point of the nerve can therefore be assigned with certainty to physical change, and this no matter whether the disturbance at each point thus affected involves chemical change, such as the decomposition of a carbohydrate or a fatty side chain, or physico-chemical change such as the disruption of some adsorption complex, or purely physical change such as the conferring of new motion upon matter in solution. There is, in fact, no experimental datum which would enable us to think of any other factor than physical change as responsible for the transmission of the excited state from point to point. We are, therefore, debarred from accepting in this case many of the mechanisms which have been suggested, such as, for example, the transference of an oxygen atom from side chain to side chain of an excited giant molecule.

Compelled thus to retreat to physical change alone, there can be little doubt as to the nature of the physical change which is responsible. Most careful experimental inquiry has failed to obtain any evidence of heat-production such as occurs in the train of gunpowder. As to the occurrence of an electrical change of very considerable magnitude, such as has been most beautifully measured by Gotch and Burch, there is no question. This in fact is the only kind of change which has been found to accompany the transit of a nervous impulse. The point, therefore, which has seemed long to Hermann and others of capital importance should be stated boldly. *No matter what may be the complete change at each excited point, its transference from point to point is accomplished by electrical agency.* To this statement the absence of any temperature change enables us to make an important addition. This excited state which is propagated by electrical change is certainly not a chemical process such as is attended with a consumption of oxygen, nor with the transit of oxygen from less stable to more stable combination. And this is equivalent to saying that, whereas oxygen may play a considerable part in the maintenance of the normal state of nerve, it plays no part in its function. We are obliged, therefore, to consider the case of nerve apart from the case of muscle, where each functional display is attended with a production of heat and a discharge of carbonic acid. But is this statement as true as it at first sight appears? In muscle function there are two clearly separable phenomena, the propagation of an electrical change and the consequent contraction. The propagation of electrical change is undoubtedly a process of the same rank as the process studied in nerve. With regard to this moiety of muscle function wherein muscle resembles nerve, there is likewise no evidence of any production of heat or output of waste product. The electrical change is over before the occurrence of that functional display which is usually thought to be associated with these factors. In the case of muscle, when acting as nerve, the facts are obscured by a later exhibition of another function. In the case of nerve itself the facts are clear. There is nothing but an electrical change observable.

It is not marvellous in view of such evidence that investigators have been found bold enough to plan a line of experimental attack upon the mysteries of nerve function, based primarily upon the assumption that the materials present in nerve are important solely as conductors, insulators, dielectrics. This is a very different assumption from that underlying the "biogen molecule," and yet in this case it has proved of the utmost value. If the purely physical concept of nerve function is finally set on one side, it will be set on one side as the result of evidence collected upon these lines. Some of this evidence has favoured such a concept, some of it has served materially to limit its range. The peculiarities of the electrical conductivity of nerve have been closely studied, sometimes deliberately, sometimes as a series of data which would one day acquire biological interest in connection with the characters of protoplasm. Both sets of workers have used the same methods. An electrical current is passed through a nerve and data are collected from the "polarised" region as also from the extrapolar stretches. For instance, in the anodal extrapolar region each point nearer to the pole acts as if at a higher potential to points more remote; in the kathodal extrapolar region near points act as if at a lower potential than points more remote.

Now, when an attempt is made to explain these facts, there is no doubt but that we must first consider all the peculiarities of the complex arrangement of electrical conductors represented by the nerve-trunk. Until that is done few will listen to the appeal: let us be simple, we are studying life. Physical models built of materials of different conductivity have been constructed to illustrate the peculiarities found. These models form a physical scheme for a simplified conception of the arrangements of conductors within the nerve-trunk. The inquiry is then pushed further. Can electrical impulses be propagated along such models? Certainly. Well then, are we to consider the nervous impulse as a phenomenon of a type akin to these? Boruttau, assiduous worker upon the electrical phenomena of nerve and upon such illustrative models—that is to say, an examiner of both sides of this question—answers in the affirmative.

Now, before deciding the extent of the reliance we will place upon this answer, we must note an important fact. Nervous impulses, whatever their essential nature, are propagated by electrical agency. They are also propagated along contiguous fibres in different directions without in any way modifying one another. Nerve-fibres therefore represent isolated conduction, and, as we have said, this entails electrical insulation. That this insulation is by no means perfect follows from the fact that electrical currents can be made to traverse nerve-fibres, and also that the electrical phenomena occurring within the fibre are demonstrable upon its surface. It might easily be shown, however, that this imperfection as revealed in both of these facts is of such a kind as to confirm the main statement when put in a slightly different form. The sheaths of nerve-fibres profoundly modify the motion of electrolytes. It follows therefore, no matter what may be the nature of the excited state of nerve, that the study of the electrical conductivity of nerve must be expected to develop information such as will be gained from the examination of any set of imperfectly insulated conductors. The core-model can be foreseen, and its invention cannot be at once accepted as revealing essential facts. It is not enough to have become acquainted with the insulation of the central conductor. Before committing ourselves to any dogma it is necessary to have studied the character of the core. We must, in fact, find data upon which to consider the possibility that the nervous impulse is no isolated phenomenon, but one that has its analogue in the conveyance of excitation from point to point within all kinds of cell structures where insulation is neither discoverable nor theoretically required. Boruttau has appreciated this necessity. He has transferred the facts of the core-model to the central core. But for this transference he has, in my opinion, no warrant. If the core of the individual nerve-fibre does really possess a structural arrangement similar to that of the core-model composed of its several parts, that fact has yet to be demonstrated. The facts elicited so far are of a different order. Boruttau has, so to speak, abandoned a consideration of the sheath without omitting the very important facts for which this structure is responsible from the experimental data made use of to present the case in this new sheathless form. On this, and on other grounds also, we for the time being fight shy of this core-model theory of nerve function.

Do considerations such as this, then, drive us back into the arms of the biogen molecules? Certainly not at present, since the needful factors seem at least in great part physical. The core has still to be studied as a conductor of electricity, that is to say, as a solution of electrolytes. What are the electrolytes of nerve? How are they distributed within the nerve-fibre? How is the motion of electrolytes which takes place within the core during the conduction of a nervous impulse to be explained?

Now if at first sight it seems absurd to treat of this core, this strip of protoplasm which is responsible for so much, as a solution of electrolytes, let us remember our treatment of the case of the cells in the sweat-gland and in the salivary gland. In putting nerve material in such a category we do nothing new or unexpected. This criterion " solution " is one to which every cell has to be compared, and from it much information illuminating the basis of function has already been obtained. The general considerations which entail this treatment are present in nerve as elsewhere. Thus the core exerts an osmotic pressure upon the surfaces inclosing it, and this pressure is normally balanced by the pressure of the solutions outside. Alter the character of these solutions ever so little and this is at once seen.

Immerse a nerve-trunk in water or in dilute solutions, it becomes turgid, and in consequence as rigid as a stick. Immerse it in concentrated solutions, it loses in weight and becomes abnormally crenated and limp. Watched under the microscope individual fibres may be seen to undergo corresponding change. Passing in review the materials in solution within the core it is at once obvious that, as in the case of other tissues also, the number of molecules of simple bodies like the inorganic salts is overwhelmingly great in comparison to the number of the huge protein molecules with which the concept "biogen" is inextricably associated. Experiments of this type are of such a nature as to give us some knowledge of the number of molecules within the core, a number to which the inorganic salts present contribute a share so great that the contribution of other matter is negligible.[1] From such experiments there is promise therefore of obtaining a quantitative value for the inorganic salts, and that is almost equivalent to the value of the electrolytes within the core. Here, then, is a road to the knowledge immediately required to fill the gap in the data requisite for a proper discussion of the core-model theory. It is unfortunately the case, however, that this road has been shown not to be a high road. The information obtained is not of such direct value as it seems, since it has been found that a balance is not necessarily obtained by equalising the salt-content of the internal and external solutions. Such knowledge, then, is of value, but is apprised as only one of the items necessary to a complete understanding of the case.

We expectantly turn, therefore, to another method which promises to provide further information as to this core in so far as it can be treated as a solution of electrolytes. An electrode placed upon the core exposed at a cross-section of a nerve-trunk is electrically negative to a similar electrode placed upon the uninjured longitudinal surface. This fact is with great probability to be assigned to a difference in the solutions present in these two situations, and to the nature of the membrane formed by the sheath of the fibres, which limits the diffusion capable of taking place between the solutions in the interior of the nerve-trunk.

In the concentration cell so formed one of the solutions is accessible, its character well known; this is the external solution or lymph, which surrounds the fibres and bathes their longitudinal surface. Modifications in this external solution produce modifications in the electromotive force of the concentration cell. Such modifications have been carefully studied, and it has been shown that they are quantitatively consistent with this assumption made as to the nature of the source of E.M.F. The external solution being varied, the internal solution is found to behave as a solution of electrolytes of such constancy that the data obtained from one nerve by one variation of the external solution are capable of accurate contrast with the data obtained from another nerve with another variation. The facts are so definite, indeed, that it is possible in this way to determine the concentration of a solution, by placing it upon the surface of a nerve instead of the normal external solution and observing the alteration produced in the E.M.F. of this concentration-cell. Here, then, is another road along which to obtain a knowledge of the internal solution of electrolytes. Given one condition it can obviously be made a high road to their quantitative determination. If the specific nature of these electrolytes were known, then that strength of their solution which would reduce this E.M.F. to zero would coincide with the strength of the internal solution. In the experimental work done in this subject this point has been realised. There is evidence, recently strongly reinforced by the use of microchemical methods introduced by Macallum, that the electrolyte concerned is potassium chloride. Doubtless this point, its importance once realised, will be settled by such direct determinations of the salts in nerve as is now being undertaken by Alcock. It is significant of the times and of the ideas which have been introduced in competition with such concepts as "biogen molecules," that so much effort is being expended upon the decision of this question. Assuming this internal electrolyte to be potassium chloride, then it has been shown that the solution present within the nerve-fibre is of such an extraordinary concentration that it is impossible to think of such a concentration as normally present there. Here then we have a handsome paradox, but one for which there is possibly a clear explanation.

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[1] Carbonic acid molecules are not considered in this case, since the surfaces are permeable to them.

When nerve-fibres are injured as by a cross-section, they are excited. If it is assumed that the excitation is a fatal one, from which the fibres do not recover, there is then present at such cross-sections a stationary excitation. Now we have shown that the transference of excitation is a matter definitely to be set on one side as due to an electrical agency—that is to say to a motion of electrolytes. Since we must think of this motion of electrolytes as produced by an alteration of the character or quantity of electrolytes present at an excited point, we may expect to find at a fatally excited point the new or additional electrolytes thus known to be characteristic of this state.

There is no evidence that the nature of the electrolytes is new. Here we are down upon an old bone of contention. It has been suspected that a decomposition process occurred at such injured points attended with an output of carbonic acid and waste products of a similar kind. There is, however, no acidity to be detected. If there were, the amount necessary to account for the phenomenon would have to rise to a value instantly detectable. This is shown by the fact that this injury current, which may be modified by alkali as by any other electrolyte, is not annihilated by a value of caustic soda solution below 0·8 per cent., and that solutions of hydrochloric acid may equally well be used for this annihilation. Place this beside the fact that it is possible to identify the additional potassium evoked by the injury by microchemical means, and it seems certain that injury produces not an electrolyte of a new character but an additional quantity of such electrolytes as were already present. A study of the injury current therefore may be taken to have revealed the existence of a solution of extraordinary concentration in the excited region of the nerve-fibre. It seems obvious that excitation may modify the strength of the solution present in one of two ways—either by withdrawal of water for combination with some more solid material not to be reckoned as part of the "solution," *e.g.* in a solid phase, or by release of potassium salt from under cover of some such solid phase into the quantity of material to which the general character of "aqueous solution" is due, or from some state of chemical combination.

The terms in which the last sentence are couched are the result of a microscopical study of the core of the nerve-fibre. It is impossible long to pursue a study of nerve-fibre structure without being impressed by the colloidal character of the solution within the core. On immersing fibres in solutions of different concentrations attention is at once drawn to the precipitations and re-entrance into a state of solution of the colloid material present. Such variations have also been observed by Höber in nerve-fibres treated with solutions of electrolytes, and have been inferred as of probable occurrence by Matthews, Greeley, Loeb, Lillie, and others. Nor is there any need to vary the character or concentration of the surrounding solution to observe these effects, since a distribution of varied states of colloidal solution is discoverable in nerve-fibres immersed in the solution usually first made use of, such as "normal saline" or "Ringer," solutions somewhere about the concentration of a decinormal solution. The states thus observed have a definite relation to injury and to the injury current which arises from it. At the cut end, the source of this current, there is some precipitation of colloid matter from solution; this portion is limited by a stretch of limpid solution, and this is again succeeded as we reach kathodal points, where the current is leaving the nerve-fibre to enter the surrounding solutions, by successive tracts showing greater and greater degrees of precipitation.

But this is an observation pregnant with suggestion, since the conditions present at "kathodal points" are as of great an interest as those present at the injured region. If there were hesitancy in postulating something of the nature of excitation as influencing the conditions due to injury, there can be none in case of the kathode. The institution of the kathodal condition has been shown to be the cause of that excitation which follows the admission of an electrical current into a nerve. During the closure of the current the whole region of the kathode is in a state of increased excitability. It is significant, therefore, that at such points there is again a visible alteration in the core. The importance of this fact is enhanced by microchemical proof that in this district also there is present a solution of a potassium salt of much greater concentration than that to be found in any other part of the nerve-fibre except the region of injury. There is therefore some basis for the statement, that *at every excited point there is a coarser aggregation of colloid material, accompanied by the appearance of a new quantity of potassium salt in a state of simple aqueous solution.*

Apparently, therefore, the facts discoverable under these headings of "injury" and "kathodal state," and the circumstances inferred from this as characteristic of excitation, are of the same order as those observed as a consequence of the excitation of extracellular material—as, for example, in the case of bone matrix, in which the setting of the matrix was attended with a demonstration of calcium salts.

It is necessary to explain at this stage an omission, which to the expert may seem of much account, namely, the absence of any reference to the finer details of the minute structure of the core. Histologists, whose views of structure are too frequently obtained from tissues altered by the precipitating effects of "fixatives," describe in this core long lines of a more refractive material which run parallel one with another and are separated by and surrounded with material of a simpler kind. The critic may say that the considerations which have taken us within the core should have taken us further. The point assumes importance since from several sides these neurofibrils have been accredited with the functions of the fibre. I have myself made theoretical use of such structures, but have been compelled to abandon them in consequence of a prolonged acquaintance with the appearance of nerve-fibres immersed in the fresh state in simple saline solutions. Neurofibrils are not seen under such conditions. This being the case, their admission into the summary of experimental evidence is hardly justified. It will be remembered that in the case of bone-formation fibrils are precipitated in the material as it sets, and that their arrangement is possibly assignable to forces in action at the moment of setting. It is possible that neurofibrils are similarly formed. If so, it is also possible that they are formed at a time when the setting of the colloidal solution of the nerve-fibre has attained a degree not arrived at during normal functional life.

Here at last, at the end of the evidence, one feels the demand for a constructive policy to guide further experimental work. If biogen molecules and "ion proteids"—the latter representing a concession, it is true—obscure many points of physical interest in the structure and function of nerve-fibres, and if the core-model theory is set on one side whilst a debate is arranged as to the nature and meaning of neurofibrils, what conception can be placed in their stead? Is there any "opening" along which the game can be further played with as much success as along the openings thus discredited? This is a claim which I have ventured to satisfy.

Let the strip of protoplasm forming the core of the nerve-fibre be thought of, not as a homogeneous mass of similar molecules, but as a *solution* in which co-exist molecules of very different sizes and kinds. For simplicity let us fix our attention upon two kinds of molecules exhibiting these differences in their utmost extreme—one kind large colloid molecules tending to form aggregates, the other kind minute inorganic salt molecules and ions mutually avoiding one another but tending to be drawn into association with colloid aggregates. Imagine also that a certain average size of aggregate represents the normal condition of colloid solution in the nerve-fibre, but that departures from this average occur as a consequence of physical change or stimulation. The observation of precipitates at excited points justifies the hypothesis that an increase in this average size is a characteristic of excitation. Now let us suppose that these aggregates or solid phases, or—less correctly, but offering a readier picture—solid particles, attract the salt molecules to their surfaces, so that layers of a condensed salt solution are found thereon. It follows that, when excitation takes place and the number of solid particles is diminished, they in this new condition must offer a smaller total surface for the retention of such a condensed solution of inorganic salts. As a consequence a new mass of inorganic salt will have found its way into the general bulk of aqueous solution surrounding the colloid masses. We thus obtain a picture of the excited state in a form which satisfies all the experimental evidence, and the picture at the same time lends itself to a clear representation of the mode of propagation of the excited state—*i.e.* nerve impulse. To ensure the propagation of such a state in the manner observed in nerve, all that is necessary is to postulate that the exciting negative anion of the inorganic salt present should have a greater velocity than the positive kation. The salt is unmasked, it diffuses, the next segment is rendered negative, desolution accompanied by the unmasking of a further quantity of salt in this new segment, further diffusion, etc., etc.

Now if I am asked at what rate this change would be propagated—and this is a question of great importance—unprovided myself with more than vague uncertain murmurings I deliberately steal another's thunder. W. Sutherland has conceived a physico-chemical explanation of the nature of the state of colloid solution, and of the nature of the nervous impulse. The molecules capable of entering the state of colloid solution are possessed of pairs of unsatisfied valencies carrying equal quantities of electrical charge of opposite sign. By reason of this quality these molecules can unite with one another to form giant molecules in which the original units are seen as "semplars" joined end to end or side to side, forming a long frame, around which and in the interstices of which the solvent lies. These giant molecules, and the core of the nerve-fibre is one such, being elastic respond to a shearing strain by the transmission of motion along the mass of the molecule. This transmitted state represents the nervous impulse, and at first apparently by a purely mechanical conception. But in the propagation of this strain opposite electrical charges are supposed in each segment of the molecule to be moved one upon the other. Upon such a basis Sutherland has worked out the probable rate of transmission of such a process, and finds it of the same order as the transmission rate of the nervous impulse. To me it seems that the mathematical treatment of this hypothesis involves considerations of exactly the same rank as those involved in the hypothesis I have advanced. The alteration supposed to occur in the colloid aggregates compares with the molar charges assumed to occur in the framework of the giant molecule, and there is the exactly analogous displacement of electrical charges, and in both cases that is all.

Should Sutherland's conception of the nature of the nervous impulse, or should mine, appear too bald or too far removed from considerations of biological rank, I would suggest that this function of transmitting change is of all the functions of living matter the most widespread and the most simple. It is probable that a similar change is transmissible within the limits of every cell in the body. This fact—and I would make bold to say that it is a fact—is frequently lost sight of in admiration of the complex results obtained as a consequence of the transmission of these changes into districts where more complex happenings occur. The conduction of nervous impulses is sometimes discussed side by side with the precise value of states of consciousness, although there is no evidence that the actual process by which change is propagated has altered in the course of development from the protozoon to man.

THE YEAR'S VERTEBRATE PALÆONTOLOGY

BY R. LYDEKKER, F.R.S.

THE following article is written on very similar lines to the one dealing with the same subject in this journal a year ago; and the introductory remarks in the latter will in the main apply in the present instance. It may, however, be well to repeat the statement that the publications referred to do not (and from the nature of the case cannot) represent anything like a complete record of the year's work in the palæontology of vertebrates. They are, in fact, merely the more important of those which have come under the writer's personal notice up to the date of sending the proof of the article to press. The opportunity has been taken to refer to a few papers published in 1906 which had not come to hand when the article for that year was compiled.

As was the case last year, there appears to be no startling or epoch-making discovery in this branch of palæontology to record; although a large amount of valuable work, either in describing new forms, or (which is at least equally important) adding to our knowledge of those already known to science, has been accomplished. From the standpoint of geographical distribution, the most important event of the year in the present department of science is undoubtedly the discovery of remains akin to the golden moles of Southern Africa in the Tertiary rocks of North America; a discovery which largely aids in explaining the anomalous distribution of this and the kindred families of the Insectivora.

Commencing with papers dealing with stratigraphical and faunistic palæontology, reference may first of all be made to one by Prof. H. Osborn, published in the *Bulletin* of the American Museum of Natural History, vol. xxiii. p. 237, on the Tertiary mammalian horizons of North America. Although confessedly a preliminary introduction to a fuller work, this paper gives much valuable information with regard to the correlation and geological ages of the various beds; a noticeable feature being the introduction of diagrammatic sketches of typical local sections in the Rocky Mountain basin and the Bad Lands of Nebraska and Dakota, by means of which the equivalence of the various strata can be seen at a glance.

Closely connected with the foregoing is an article in the May number of *The American Journal of Science*, by Mr. F. B. Loomis, on the probable mode of origin of the Wasatch Eocene deposits. The relative scarcity of fish-remains forbids, in the author's opinion, the view that these beds were deposited in lake-basins. Nevertheless the occurrence of remains of crocodiles, freshwater terrapins, and fishes in sufficient numbers to make up 10 per cent. of the whole fauna, would be very remarkable in strata of æolian origin; and the presence during deposition of a certain amount of water seems therefore to be essential. It is accordingly suggested that the Wasatch beds were laid down on plains subject to periodical inundations; confirmation of this being afforded by their lithological constituents.

Californian cavern exploration has been continued by Mr. E. L. Furlong, who in a note to the March number of *Science* communicates the results of a preliminary examination of a cave near Auburn. The remains found included those of the ground-sloth *Megalonyx*, as well as of pumas and horses; but no traces were discovered of the extinct ruminants *Euceratherium* and *Preptoceras* characteristic of the Shasta caves explored by the same gentleman a few years ago.

In a paper published in the *Annals* of the Carnegie Museum, vol. iv. No. 1, 1906, Mr. O. A. Peterson describes a number of new mammals from the Miocene of Nebraska and Wyoming. Several of these belong to the group of oreodonts or merycoidodonts (the "ruminating hogs" of Leidy), but there is also a primitive camel, as well as a dog-like carnivore of the genus *Amphicyon*. The Miocene fauna of South Dakota has occupied the attention of Dr. W. D. Matthew, who has published the results of his investigations in the *Bulletin* of the American Museum of Natural History. The contents of this paper are noticed later.

In Europe Dr. Max Schlosser, in the *Neues Jahrbuch* (1907, vol. ii. p. 1), has given descriptions of fossil mammals from the Pliocene of Spain, with observations on the line of division between that epoch and the Miocene. A similar service has been accomplished by Mr. F. Roman (*Comm. Geol. Portugal*, 1907) in regard to the mammalian fauna of the later Tertiary strata on the right bank of the lower part of the Tagus valley. In addition to remains of *Mastodon*, *Hipparion*, etc., the author has described those of an apparently new species of rhinoceros. Notices of later Tertiary mammals from Hungary will be found in a paper by Mr. W. Güll, and others, published in the *Mitteilungen Ungar. geol. Anstalt*, vol. xiv. p. 283. Similar brief mention will suffice for a paper by Mr. A. Zdarsky on the Tertiary mammal fauna of Eibiswald, published in the *Jahrbuch* of the Austrian Geological Survey (vol. lvii. p. 437).

A work of an altogether unique type is Mr. Charles Depéret's *Les Transformations du Monde Animal* (Paris, 1907). Its main object is to discuss our present knowledge of the laws regulating the modifications of animals, from the date of the first appearance of life on the globe to the present day. After a preliminary review of the rise of modern ideas with regard to evolution, the author discusses the variability of species in space and time, the constituent elements of phylogenetic "trees," the causes of the extinction of species, the formation of new types, and, finally, the important *rôle* played by migration in the evolution of faunas.

During the year the vertebrate fossils of the Fayûm district of Egypt have attracted American collectors; and to the October number of *The Century Magazine* Prof. H. F. Osborn contributes an illustrated article describing his experiences while in search of such remains, with remarks on the nature and origin of the fauna and their bearing on the geographical distribution of mammals. Among the illustrations, attention may be directed to restorations of *Arsinöitherium*, *Hyænodon*, and *Zeuglodon*. In Eocene times the Fayûm, in the author's opinion, was a savanna-country, partly open, partly covered with scrub, and partly with forest; the temperature being much the same as at the present day. That Africa (then much less extended to the north than at the present day) was the home of the ancestral proboscideans, sea-cows, hyraxes, and probably hyænodonts, Prof. Osborn is convinced; but the absence in the Eocene deposits of remains of primitive hippopotamuses, ruminants, horses, and rhinoceroses, leads to the further inference that "none of these quadrupeds had as yet reached

Africa; that they were evolving elsewhere, either in Europe, Asia, or North America, and preparing for the great interchange of life which would occur when Africa should again be connected with the other continents."

The explorations carried on in the Fayûm by Dr. C. W. Andrews resulted in the acquisition of a few specimens of interest, one of which (as mentioned in *The Geological Magazine* for March) served to demonstrate that the supposed genus *Phiomia* is really based on a portion of the lower jaw of a young individual of a species of the proboscidean genus *Palæomastodon* retaining the milk-teeth. Very curious is the discovery of the existence of a huge globe-like chamber on the side of the lower jaw of *Geniohyus*, which in life may have contained a gland. There are certain indications that this genus, which was originally regarded as one of the Suidæ, may be related to the hyraxes—an interpretation which would accord best with Prof. Osborn's view. The existence in the Fayum Eocene of remains of a large bird related to the herons is a discovery of considerable interest.

Egypt is, however, by no means the only part of Africa from which discoveries of fossil vertebrates have been recorded during the period under review; and from the fact that mammalian remains have been described from three distinct localities at the opposite extremity of that continent, we may expect in the future to obtain further important information with regard to the past history of the South African fauna. The first of the papers referred to is published in the final report of a recent geological survey of Natal and Zululand, in which Dr. W. B. Scott, of Princeton, New Jersey, gives a description of the two last lower molars of an extinct elephant obtained, in company with remains of rhinoceros, hippopotamus, and antelopes, from a deposit of late Tertiary age in Zululand. The elephant, for which the author proposes the name *Elephas zulu*, has the constituent plates of its molar teeth more numerous and thinner than those of the existing African species. They are described as being to a great extent intermediate in this respect between the latter and those of the extinct European and Asiatic *E. antiquus*; but according to the figures they seem much nearer the molars of the species last named. It is suggested that *E. zulu* may have been the ancestor of the living *E. africanus*, in which case it would almost be imperative to regard the molars of the latter as being of a degenerate type. This question requires careful consideration; but, apart from this, the discovery is one of great interest.

The diamond-diggings at Kimberley are the place of origin of the second batch of remains, which have been described by Dr. E. Fraas of Stuttgart in the *Zeits. deutsch. Geol. Ges.* for 1907 (pp. 232–43). The specimens include an imperfect mastodon tooth, probably belonging to the same species as the one described last year from Barkley West; and likewise other teeth referable to a zebra, a hartebeest or blesbok, and a hippopotamus. In most instances no attempt is made at specific determination, but the author refers the hippopotamus remains to a large race of the common African species.

The third discovery, reported by Messrs. F. Mendell and E. C. Chubb in *The Geological Magazine* (pp. 443–8), relates to Rhodesia, where remains of existing African mammals have been found associated with stone implements of a palæolithic type.

Passing on to a survey of papers devoted more or less exclusively to particular groups of mammals, brief reference must suffice to one by Dr. F. Ameghino of Buenos Aires in which the author claims man to be of South American origin, his ultimate ancestor being the Tertiary opossum-like genus *Microbiotherium.* Such a phylogeny is not likely to be accepted by naturalists. This paper was published at La Plata.

In March Mr. H. F. Standing read a paper before the Zoological Society of London on extinct Malagasy lemurs, in which he discussed their relations to living lemurs and the higher Primates. The remains were obtained in the muddy bed of a swamp formed by the blocking-up of the River Mazy by a lava-flow, at from a few inches to three or four feet below the surface. They consisted of a large number of skulls and limb-bones of lemurs and lemur-like animals. This material enabled the author to corroborate the view, previously put forward by Dr. Forsyth Major, that the extinct lemurs of Madagascar were, in many respects, intermediate between existing lemurs and monkeys, and to express his belief that New World monkeys and the Lemuridæ, as well as the Malagasy Indrisinæ, had a common origin. He also stated his opinion that, in view of recent additions to our knowledge of lemuroids, and from the evidence of the new collection as to their close relationship to apes, it was no longer possible to separate the Primates into the suborders Lemuroidea and Anthropoidea. The full text of this communication was not published at the time when the present article was written.

Practically nothing has been accomplished during the year to add to our scant knowledge of the past history of bats. It is true that Mr. G. E. Mason, in the September issue of *The Annals and Magazine of Natural History*, described the remains of a supposed new fruit-bat from Round Island, near Mauritius. These remains occur in a guano-deposit, and appear to be very recent; and in a note on Mr. Mason's communication published in the October number of the same journal, Dr. Knud Andersen pointed out that they appear to be inseparable from the existing *Pteropus rodricensis.*

On the other hand, some very important evidence has been obtained with regard to the palæontology and past distribution of one group of Insectivora. The golden moles (Chrysochloridæ) form at the present day a group entirely confined to Southern and South-Eastern Africa, whose nearest relatives are apparently the tenrecs of Madagascar. An extinct Patagonian insectivorous mammal (*Necrolestes*) has, however, been regarded as a member of the same group; and, more recently, Dr. W. D. Matthew (*Science*, December 14, 1906, and *Bull. Amer. Mus. Nat. Hist.*, vol. xxiii. art. 9, 1907) has announced the discovery in the Miocene strata of South Dakota of the remains of what he regards as an undoubted golden mole, although referable to an extinct genus (*Arctoryctes*). The author also considers that the North American Tertiary genus *Xenotherium*, previously regarded provisionally as a monotreme, is a member of the same group. If the identifications be trustworthy, the discovery is of much interest from the standpoint of geographical distribution. Although its bearings cannot be fully discussed here, it refutes the idea that the Patagonian *Necrolestes* affords any evidence in favour of a former Antarctic land-connection between Africa and South America.

In the paper on the Lower Miocene fauna of South Dakota referred to above, Dr. Matthew, in addition to describing certain new species, discusses the relationship of the Tertiary Canidæ to their existing representatives. In his opinion the Old World *Cyon* and probably the South American *Speothos* (*Icticyon*) are derived from *Temnocyon* of the John Day Tertiary; the characters of the skull and skeleton confirming the evidence afforded by the dentition. The more typical South American Canidæ appear, on the other hand, to be the nearest living representatives of the middle Tertiary *Nothocyon* and *Cynodesmus*; *Mesocyon* being slightly off the line in the direction of *Temnocyon*.

The generally accepted classification of fossil Canidæ is, moreover, in the same author's opinion, misleading; more especially the association of the genera *Cephalogale*, *Simocyon*, *Oligobunis*, *Enhydrocyon*, and *Hydrocyon* in the single subfamily Simocyoninæ. The two last-named genera are, for instance, probably not separable, and together with *Philotrox* appear to be related to *Temnocyon*, and so with the modern *Cyon*; while *Oligobunis* is probably referable to the Mustelidæ. Again, *Cephalogale*, which has been regarded as ancestral to the bears, seems rather, judging from dental characters, to be related to the typical members of the family (Caninæ); such aberrant features as it possesses in this respect being to some extent paralleled in *Cynodesmus*.

Here it may be well to quote a very important note on classification generally appended by Dr. Matthew to his observations on extinct dogs. It appears, he writes, "obviously improper to separate two closely allied genera or species because they are destined to give rise in the future to two distinct families, in the opinion of the investigator. So far as classification and nomenclature are based upon the facts of structural resemblance or difference, they are permanent, but the attempt to make families, genera, or species correspond with hypothetical phyla is not only misleading but destructive of any approach to uniformity or permanency of arrangement."

These remarks the present writer may take the opportunity of endorsing. An attempt has been made to introduce such a phylogenetic classification in the case of the early Perissodactyla, and the genera *Hyracotherium* and *Systemodon*, which are obviously near relatives, have been referred to distinct families on account of the presumption that while the one is the ancestral form of the horse tribe, the other has given origin to the tapirs.

Dr. Matthew, as already mentioned, transfers *Oligobunis*, which had been regarded as ancestral to *Speothos*, to the Mustelidæ. The short muzzle lacks the constriction in front of the carnassials distinctive of the early Canidæ, and the other dental features, especially the presence of a distinct notch between the blades of the lower carnassial, are of a musteline type. Very interesting is a short-jawed musteline described as *Megalictis*, with teeth intermediate between those of *Oligobunis* and the living *Gulo* and *Mellivora*, to which latter it appears nearly related.

Certain new rodents, some referable to the well-known beaver-like genus *Steneofiber*, and others to the allied *Euhapsis*, are also described by Dr. Matthew; but these may be passed over without further notice.

Of more general interest is *Epigaulus*, a new horned rodent from the Miocene of Kansas, described by Mr. J. W. Gidley in the *Proceedings* of the U.S. National Museum (vol. xxxii. p. 627). It is the most specialised member of the Mylagaulidæ yet discovered, with the large nasal horns placed just in front of the orbits. Mr. Gidley concludes that while this extinct group of specialised rodents has some remote affinities to the beavers (Castoridæ) and a nearer relationship to the squirrels (Sciuridæ) it has a greater number of characters in common with the sewellels (Haplodontidæ), and also shows certain resemblances in general proportions to some of the Asiatic mole-rats (Spalacidæ). The latter, however, seem due more to modification of the skeleton for burrowing than to real relationship. In tooth-development the Mylagaulidæ have surpassed in specialisation the other Sciuromorpha, and could not have been ancestral to any of the living forms.

Squirrel-like rodents of the genera *Paramys* and *Sciuravus*, from the Eocene deposits of the Wasatch and Wind Rivers, have been described during the year by Mr. F. B. Loomis (*Amer. Journ. Sci.* for February). Both genera are nearly related; the former, at any rate, exhibiting many squirrel-like characters, and being probably one of the ancestral types of the modern family.

The extermination of the urus, or aurochs—the ancient European wild ox (*Bos taurus primigenius*)—forms the subject of a very interesting paper by Dr. A. Mertens published in the *Abhandlungen und Berichte* of the Magdeburg Museum. The author confirms the opinion that the name aurochs belongs to this animal, although it has been misapplied to the bison. It is likewise certain that in the time of Herberstain (the middle of the sixteenth century) aurochs were living in Poland, and were seen alive by him; and, according to other testimony, a herd of thirty was living in the Jaktorowka (or Wiskitki) forest of the Masovia district of Poland in the year 1564. By 1599 the number was reduced to twenty-four, while in 1602 only four remained, these being reduced in 1620 to one cow, which appears to have been killed seven years later. A few half-domesticated individuals were, however, living in captivity in 1627. Herberstain's statement that the aurochs was typically black, with a light dorsal streak, is accepted. Other evidence tends, however, to show that there were grey aurochs in Poland, and red ones in Central Germany. This is not the only paper on this subject published during the year, as Dr. M. Auerbach, in the *Verhandlungen der Naturwissenschaftlichen Vereins* of Karlsruhe (vol. xx.) has given descriptions of a number of remains of both the urus and the bison preserved in the museum of that city.

Little appears to have been contributed during the year to our knowledge of the past history of the deer tribe. A considerable collection of antlers of reindeer and elk from the Pleistocene of Olai, Livonia, has, however, been described by Mr. G. Schweder, in the *Korrespondenzblatt naturf. Vereins* of Riga, where it is pointed out that in 1831 the name of *Cervus gallinus* was suggested by Fischer for the fossil elk antlers from this district. If, therefore, the European elk be eventually split up into local races, this name will have to be considered.

In the article on vertebrate palæontology contributed to SCIENCE PROGRESS a year ago, reference was made to Dr. Lönnberg's opinion as to the near relationship of the "Irish elk" to the reindeer, and to certain arguments which had been advanced against that view. These arguments have been endorsed and strengthened in a note contributed by Dr. R. F. Scharff to the May number of *The Irish Naturalist.*

If the work on fossil Cervidæ has been small and unimportant, that accomplished in America in connection with the extinct ruminating oreodonts, or merycoidodonts, and fossil swine has been extensive. Some of these merycoidodonts are described in the paper by Mr. Peterson already referred to; but by far the most interesting is one from the Miocene of Nebraska, for which Mr. E. Douglass (*Annals* of the Carnegie Museum, vol. iv. No. 2, 1907) proposes the name of *Pronomotherium.* The skull is characterised by its shortness, the presence of a small pair of horns above the orbits and of a large cavity in advance of the same, as well as by the extraordinary depth of the hind part of the lower jaw. In the opinion of Mr. Douglass, the owner of this skull was furnished with a proboscis of considerable length. The development of horns is probably a sign that the genus belonged to a decadent, or over-specialised, member of the group. Another member of the same genus is described by the author in the *Bulletin* of the American Museum, vol. xxiii. art. 32. Skulls of a number of other forms of these curious "ruminating hogs" are described in the same two papers, but since they belong to well-known genera, further mention is needless.

The work on the swine group is suggestive of somewhat unnecessary genus-making. In a paper published in the *Memoirs* of the Carnegie Museum (vol. ii., No. 8) Mr. O. A. Peterson described a peccary from the Miocene of Nebraska under the name of *Thinohyus siouxensis.* According, however, to Dr. Matthew, *Thinohyus* is inseparable from the White River genus *Perchœrus*; but instead of referring Peterson's species to that genus, he proposes the new generic name *Desmathyus* for a more or less closely allied animal, and regards "*Thinohyus*" *siouxensis* as a primitive aberrant form transitional from *Perchœrus.* Surely in such a case it would be better to include all three forms in one genus. In these Miocene and Oligocene peccaries there were three pairs of upper incisor teeth, instead of the two of the modern *Dicotyles*; but in some of the Miocene species the outer pair is much reduced in size. These later Miocene forms also agree with modern peccaries in having the tympanic bulla of the skull filled with cancellous bony tissue, whereas in the typical *Perchœrus* it is empty.

The evolution of the horse and the mutual relationships of the different domesticated breeds are subjects which continue to attract the attention of investigators on both sides of the Atlantic. Dr. R. S. Lull has drawn up a useful summary of the main facts connected with the evolution of the horse family, which first appeared in the March number of *The American Journal of Science*, but has been reprinted in pamphlet form as a guide-book to the collection in the Peabody Museum at Yale University. Prof. J. C. Ewart, on the other hand, has devoted his attention to a large series of horse-skulls discovered in the Roman fort at Newstead, near Melrose, and published the results of his investigation in the *Transactions* of the Royal Society of Edinburgh, with a summary in an article in the

April number of *The Quarterly Review*. On the evidence of these skulls Mr. Ewart proposes to recognise three types of domesticated horse, severally distinguished by the degree of inclination of the face to the basal axis of the cranium.

During the year Dr. Ameghino has published in the *Anales* of the Buenos Aires Museum (vol. xvi.) a figure of the skeleton of *Hippidium*, a small extinct South American horse remarkable for the great length of the nasal bones and of the slits by which they are separated from the adjacent elements of the skull. A model of the skeleton from which Dr. Ameghino's figure is taken has been installed in the British Museum (Natural History).

A new rhinoceros from Portugal has been named by Mr. Roman in the paper cited above, and Mr. F. Toula (*Jahrb. Geol. Reichsanstalt*, vol. lxvi.) records a new variety of *Rhinoceros mercki* from Austria.

Brief mention may here be made of another paper by Dr. Ameghino in the serial just quoted, where it is pointed out that the skulls of some of the South American toxodonts are furnished with rudimentary horn-like prominences.

As regards the proboscidean group, reference has already been made to the discovery of an extinct elephant and mastodon in South Africa; and it should be added that Dr. Schlosser, in a paper quoted above, has recorded remains of *Mastodon longirostris* from the upper Tertiary of Spain. To the energy of Miss Dorothea Bate science is indebted for the discovery of remains of a pigmy elephant (*Elephas cretensis*) in the caves of Crete; these having been described and figured by their discoverer in the August issue of the Zoological Society's *Proceedings*. To the exhibition galleries of the American Museum has been added a complete skeleton of the Columbian mammoth, discovered in Indiana in 1903. According to a preliminary description by Prof. H. F. Osborn published in the *Bulletin* of the American Museum (vol. xxiii. p. 255), the mounted skeleton stands 10 ft. 6 in. at the shoulder. The largest known tusk of this species or race of mammoth appears to be one referred to in *Science* for 1907 (vol. xxv. p. 971) by Mr. C. H. Sternberg, of which the exposed portion measured 14 ft. in length, with a basal diameter of 8 in.

Of the few papers on fossil cetaceans which have come under the writer's notice, one by Mr. F. W. True, issued as No. 1694 of the quarto series of publications of the

Smithsonian Institution, is devoted to an imperfect skull obtained in 1847 from the Eocene marl of the Ashley River, South Carolina. In the year of its discovery appeared a brief account of the specimen by Mr. M. Tuomey, who referred it to *Zeuglodon*; and two years later it was named *Z. pygmæus* by Prof. J. Müller. The specimen afterwards came under the notice of Prof. L. Agassiz, who caused a plate to be prepared, with the lettering *Phocodon holmesi*; but for some reason this plate was never issued, and in 1895 Prof. E. D. Cope referred the specimen to a new genus, under the name of *Agorophius pygmæus.* Despite the fact that when first figured the specimen had a single *Squalodon*-like tooth in the maxilla, a suggestion was made that the species might be an ancestral rorqual. In Mr. True's opinion, *Agorophius* is, however, a squalodont, differing in cranial characters from *Squalodon* itself. The European *Squalodon ehrlichii* has a broad rostrum recalling the Carolina genus, and may be a connecting link between *Squalodon* and *Agorophius.* The type specimen of another American Tertiary cetacean—*Anoplonassa forcipata*—has also been redescribed by Mr. True (*Bull. Mus. Zool. Harvard Coll.*, vol. li. p. 97), who regards it as representing a member of the Physeteridæ allied to the modern *Mesoplodon.* The rarity of cetacean remains in the Eocene clay of Barton, Hampshire, fully justifies Dr. C. W. Andreas in describing (*Quart. Journ. Geol. Soc.*, vol. lxiii. p. 124) a vertebra of *Zeuglodon wanklyni*; this being the third known specimen of that species. Of the two earlier ones, the second was incorrectly referred to a rorqual, under the name of *Balæonoptera juddi.* Of greater importance is a memoir by Dr. O. Abel, published in the *Denkschriften* of the Vienna Academy (vol. lxxxvi.), on the rudimentary pelvis of cetaceans. At the conclusion of this memoir the author points out that the development of a caudal fin in cetaceans and sirenians has rendered a functional pelvis superfluous in both groups. Among cetaceans and dugongs the reduction has followed parallel lines, culminating in a retention of portions of the ilium and ischium. On the other hand, the manatis have followed a line of their own, and have retained only the ischium.

The only important work on fossil marsupials which has come under the writer's notice is an attempt by Dr. E. C. Stirling (*Nature*, vol. lxxvi. p. 543) to restore the external form of *Diprotodon.* As regards general contour, Dr. Stirling has followed the lines of a wombat, although with a certain increase in the relative length of the limbs. Since, however, the teeth and fore part of the skull are of the kangaroo type, with some indications of a greater development of the soft parts of the nasal region, the peculiar puffy and cushion-like muzzle of the kangaroo has been introduced, in a somewhat accentuated degree, into the restoration.

Dr. Broom's recent work on the ancestry of mammals receives mention at the end of the section on reptiles.

Work on fossil birds during the period under review appears, as usual, to have been but small, The discovery of a leg-bone of a heron-like species in the Eocene of Egypt has been already mentioned. Another lower Tertiary bird has been identified by Dr. O. Abel (*Centralblatt für Mineralogie*, 1907, p. 450) in the shape of a large coracoid from the upper Eocene of Choctaw County, Alabama, which had been mistaken for a zeuglodont bone. That this bird, for which the name *Alabamornis gigantea* has been suggested, was of huge size, and therefore flightless, is certain; but whether it was related to *Diatryma* of the North American and *Gastornis* and *Remiornis* of the European Eocene must for the present remain doubtful.

In connection with birds, reference may be made to an exceedingly able and interesting paper on the origin of flight in vertebrates by Baron Francis Nopcsa, published in the June issue of the *Proceedings* of the Zoological Society of London. In the opinion of the author, bats and pterodactyles are the descendants of four-limbed arboreal creatures in which, owing to the development of a flying-membrane (*patagium*), the fore-legs had become to a certain degree adapted for flight, and in consequence less well suited for terrestrial progression. Birds, on the other hand, are regarded as having been evolved from running bipedal dinosaur-like reptiles, in which the front limbs, owing to a flapping movement, became modified into wings, without any concomitant loss of the cursorial power of the hind-limbs. It is on account of this superior mode of development that birds have outstripped both pterodactyles and bats in the contest for the "command of the air." They may be likened to "äeroplanes," whereas their rivals have not passed the "air-ship" stage. Baron Nopcsa's paper is illustrated with a restoration of a cursorial "prŏavis."

From the preceding paragraph we are led by an easy transition to pterodactyles, on which group, as represented in the upper Jurassic strata of Swabia, Dr. Felix Plieninger has contributed an important memoir to the Stuttgart *Palæontographica* (vol. liii., Nos. 4–6). Several beautifully preserved skeletons from the Lithographic Stone of Nusplingen and other Swabian localities are figured, for one of which the new name *Rhamphorhynchus kokeni* is proposed. The generic position of the English *Scaphirhynchus purdoni* is also discussed at some length.

Having completed the survey of the extra-European Triassic dinosaurs, Prof. F. von Huene has commenced in *Geologische und Palæontologische Abhandlungen* (Jena, 1907) a detailed description of their European representatives. The first part is devoted to the dinosaurian remains from the Keuper of the Nürenberg district, first brought to notice by Engelhardt in 1834, and afterwards referred to *Thecodontosaurus* and *Palæosaurus* of Riley and Stuchbury, which were long regarded as a general receptacle for Triassic dinosaurs of all descriptions. Dr. von Huene refers all the remains described in this part to von Meyer's genus *Plateosaurus*, of which, in addition to the typical *Pl. engelhardti* and *Pl. queustedti*, he recognises the new species *Pl. reinigeri* and *Pl. erlenbergiensis.*

A redescription of the type skeleton of the sauropod dinosaur *Morosaurus agilis* forms the subject of a paper by Mr. C. W. Gilmore in the *Proceedings* of the U.S. National Museum (vol. xxxii. p. 151), in which it is suggested, on account of the primitive character of the vertebral column, that this species may belong to the genus *Hoplocanthosaurus*. To the sauropod genus *Pelorosaurus*, typified by a humerus from the English Wealden, Mr. H. E. Sauvage (*Bull. Soc. Boulogne-sur-mer*, vol. vii.) refers part of a femur from the Jurassic of the Boulonnais; also mentioning that the teeth from the same deposit described as *Neosodon* and *Caulodon* likewise pertain to the same genus.

Dinosaurian remains from the Jurassic and (?) Cretaceous of Madagascar have been described by Mr. A. Thevenin in the *Annales de Paléontologie*, vol. ii. pt. 3. Some of these are referred to *Bothriospondylus madagascariensis*, a species described several years ago by the present writer; while others are assigned to *Titanosaurus* and *Megalosaurus*. As *Titanosaurus* is typically from the Cretaceous of Central India, its reappearance in Madagascar has an important bearing on the theory of a former land-connection between those two countries.

Great interest also attaches to a couple of skeletons of a small reptile from the Trias of Lossiemouth, Elginshire, regarded by Dr. H. Smith Woodward (*Quart. Journ. Geol. Soc.*, vol. lxiii. p. 140) as representing a new type of dinosaur, for which the name *Scleromochlus taylori* is proposed. The pelvis is unlike that of the Rhynchocephalia, while the absence of bony armour and the apparent perforation of the acetabular cavity of the pelvis distinguish the skeleton from the Parasuchia. On the other hand, the observable characteristics seem distinctly dinosaurian, and appear to indicate relationship with the Triassic American genera *Ammosaurus*, *Anchisaurus*, and *Hallopus*. The large skull, apparently toothless jaws, and the firm union of four elongated metatarsal bones are, however, peculiarities of the Elgin reptile, which was evidently a specialised type. The extreme lightness of the skeleton, coupled with the elongation of the hind-limbs, suggests leaping habits.

Passing on to the Parasuchia, or Phytosauria, we find that in America Mr. J. H. Lees has described in *The Journal of Geology* (vol. xv. p. 121) a new genus and species from the Trias of Wyoming, under the name of *Palæorhinus bransoni*. The genus is akin to the American *Rhytidodon*, from which it appears to be mainly distinguished by a difference in the form of the ilium. In Europe Prof. E. Fraas (*Jahreshefte Ver. Naturkunde Württemberg*, 1907, p. 101) has made known a new species of *Aëtosaurus* from the upper Stubensandstein of Stromberg, near Pfaffenhofen, under the name of *A. cristicauda*. In regard to the group to which these reptiles belong, it is remarked that one of the most important differences from the typical Parasuchia is the smaller share taken by the ischium and pubis in the formation of the acetabulum. This and other differences do not, however, necessitate ordinal separation from that group, of which the Aëtosauria may be regarded as a specialised branch, distinguished by the peculiar type of the dermal armour.

The acquisition by the Belgian Museum of a number of vertebrate remains from the Eocene strata of Erquelinnes, near Hainault, has enabled Dr. L. Dollo (*Bull. Soc. Belge Géol.*, vol. xxi. p. 3) to describe a new type of crocodile, to which he has given the name *Eosuchus lerichei*. Although a member of the modern group of the order, this genus, in the less backward position of the posterior nostrils, makes some approximation to Jurassic forms.

A memoir on the structure and adaptive modifications of the armourless marine Jurassic crocodiles of the genus *Metriorhynchus*, by Mr. G. von Arthauber (*Beitr. Pal. Ost.-Ung.*, vol. xix. p. 287, 1906) has given rise to a considerable amount of discussion. In the *Centralblatt für Mineralogie* (1907, p. 225) Dr. O. Abel criticised the memoir somewhat severely, and published an amended restoration of the external form of *M. jækeli*, in which the reptile is represented with flipper-like limbs and a double-lobed tail-fin. Later on in the same volume (p. 353) further criticisms are published by Mr. E. Auer. To all these Mr. von Arthauber replied in the *Centralblatt* (p. 385), where his own views are maintained; while in a second paper he gave further details with regard to the structure of the skeleton of the hind-limb, directing special attention to the arrangement of the tarsal bones. Another contribution to the osteology of the genus, as represented by *M. superciliosus* of the English Oxfordian, has been made by Mr. E. T. Leeds in *The Geological Magazine* (decade 5, vol. iv. p. 314), where attention is directed to the confusion which has arisen owing to a portion of the coracoid having been wrongly described as the scapula.

Among more typical crocodiles, Mr. R. W. Hooley (*Quart. Journ. Geol. Soc.*, vol. lxiii. p. 50) has described a fine skull and other remains of *Goniopholis crassidens*, obtained after the fall of the cliff of Wealden strata at Atherfield, Isle of Wight. The identification by Dr. A. S. Woodward (*l.c.*, p. 132) of the same genus, in the form of *G. Hartti*, in the Cretaceous rocks of Bahia, Brazil, is of considerable interest.

In the only paper on fossil snakes which has come under the writer's notice, Dr. W. Janensch (*Archiv. für Biontologie*, vol. i. p. 313) discusses the monster serpent *Pterosphenus schweinfurthi*, of the Fayum Eocene, and supports the view that it is rightly associated with the European *Palæophis* in a separate family, the Palæophidæ, which is more nearly related to the pythons than to the sea-snakes, despite the fact that its representatives were marine.

Important information with regard to the osteology of the ichthyosaurs has been furnished by Dr. C. W. Andrews in a paper on the Oxfordian *Opthalmosaurus leedsi* published in the May number of *The Geological Magazine*. This species is remarkable for the great variation exhibited by the bones of different individuals, this feature apparently indicating that these reptiles were in a state of developmental inæquilibrium. A restoration of the back of the skull has been attempted, which shows that the whole arrangement is adapted to give the greatest possible rigidity to the quadrate—doubtless for the purpose of affording a firm support for the long jaws. The stapes, which, according to the author, has lost its function as a bone of the internal ear, is firmly united at one end with the basi-occipital, whilst its other extremity is fitted into a pit-like facet of the quadrate.

This conclusion as to the stapes (or columella) having no connection with the auditory function is disputed by Dr. Louis Dollo in a note published in the *Bulletin de la Société Belge de Géologie*, vol. xxi. p. 157, who suggests that it has a kind of secondary auditory function, connected with the diving or "sounding" habits of the ichthyosaurs. Such a function he considers to be connected with a modification of the cerebral circulation and paralleled by the conditions obtaining in cetaceans.

The description by Mr. C. W. Gilmore, in the March number of *The American Journal of Science* (vol. xxiii. p. 193), of a new species of *Baptanodon* from the Jurassic of Wyoming is of interest from the fact that the remains are less incomplete than those of any other known specimen of the genus.

On account of the excessive width of the front paddle, which comprises eight longitudinal rows of bones, the skeleton of a new species of ichthyosaur (*Ichthyosaurus platydactylus*) from the Chalk of Kastendamm, Hanover, described by Mr. F. Broili in vol. liv. of the Stuttgart *Palæontographica*, is of more than ordinary interest. At the close of his memoir the author illustrates diagrammatically the fact that in the Liassic ichthyosaurs the front paddles and tail-fin are relatively much larger than in the Cretaceous species, this apparent loss in the latter of propelling power being compensated by an increase in the width of the fore-paddles.

Considerable importance attaches to an account of the Cretaceous pliosaurian genus *Brachauchenius* given by Mr. S. W. Williston in No. 1540 (vol. xxxii. p. 477) of the *Proceedings* of the United States National Museum. *Brachauchenius*, which is known from West Kansas, is regarded by its describer as closely related to *Pliosaurus*, from which it differs in having singleheaded cervical ribs. From other plesiosaurians in which the skull is fully known, it differs in that the palatines meet each other in the middle line, but this is a feature which the author thinks will be met with in *Pliosaurus*. The assumed relationship of the plesiosaurs to chelonians is disputed. The latter lack, for instance, epiphyses to the humerus, while such resemblance as exists between the shoulder-girdle in the two groups is due to adaptation. Chelonians are without the parietal foramen of plesiosaurs, and retain the hypocentral mode of articulation of the ribs, whereas in plesiosaurs the ribs are attached to the transverse processes of the vertebræ. Sauropterygia are, indeed, probably descended from theriodont ancestors, while Chelonia appear to be derived from a cotylosaurian type, both being widely sundered from ichthyosaurs and rhynchocephalians.

Brief reference will suffice to a paper by Mr. F. Broili, published in the *Centralblatt für Mineralogie*, on certain reptilian remains from the Kössen beds of the Trias of the Alps. From the form of the dorsal vertebræ and the stoutness of the abdominal ribs, the specimens evidently indicate one of the nothosaurs, or primitive sauropterygians. Their large size suggests affinity with *Partanosaurus*, but in structure the vertebræ appear to display characters intermediate between those of that genus and those of *Nothosaurus*.

In a communication to *Science* for 1906 (vol. xxiv. p. 184) Prof H. F. Osborn states that the American Museum has received from the Brazilian Coal Commission natural casts of a small Permian reptile near akin to *Stereosternum* of the same country and horizon, and to *Mesosaurus* of the South African Permian. An opinion is quoted to the effect that none of these reptiles are related to the plesiosaurs (Sauropterygia).

The huge Eocene turtle known as *Eosphargis gigas*, typically from the London Clay, also occurs in the corresponding formation of Belgium, where an almost complete specimen has been discovered at Quenast. According to Mr. Dollo (in the serial already quoted) the upper shell, or carapace, of this turtle is quite different from that of the modern leathery turtle, and is of the general type obtaining in ordinary turtles.

Remains of soft river tortoises (Trionychidæ) from various North American horizons form the subject of a paper by Mr. O. P. Hay in the *Bulletin* of the American Museum, vol. xxiii. art. 34.

The list of rhynchocephalian reptiles has been increased by Dr. R. Broom's description (*Trans. S. African Phil. Soc.*, vol. xvi. p. 379) of the new genus *Palacrodon browni*, from the Triassic division of the Karoo series of South Africa. Dr. Broom, it may be added, restricts the Rhynchocephalia to reptiles with a radiating pelvis, and therefore excludes the Indo-European Triassic genera *Palæohatteria*, *Rhynchosaurus*, and *Hyperodapedon*, in which the pelvis is plate-like. On this view, *Palacrodon* is the only Triassic representative of the order.

During the year important work has been accomplished in that remarkable group of Permian reptiles known as the Pelycosauria. In an article published in the *Bulletin* of the American Museum (vol. xxiii. p. 265), Prof. H. F. Osborn has given a figure of the skeleton of the Texan "ship-lizard," *Naosaurus claviger*, with an attempted restoration of the creature's bodily form. The length of the skeleton is 6½ ft. Among the more striking features are the enormous head, armed with powerful teeth, and the great height of the spines of the vertebræ of the long back, which are furnished with transverse bars recalling yard-arms, and thus suggesting the name of the genus. The restoration of the allied genus *Dimetrodon* has been essayed by Dr. E. C. Case in vol. xv. of *The Journal of Geology*.

Of far more importance is the monographic revision of the Pelycosauria by the last-named naturalist, published by the Carnegie Institution of Washington. After discussing the various opinions as to the proper systematic position of these reptiles, the author concludes that they really form a subordinal group of the Rhynchocephalia. They all had notochordal vertebræ, with intercentra, and two-headed ribs; but it was only in the more specialised forms that the spines of the vertebræ attained the characteristic development. All were carnivorous. The more primitive representatives of the group, constituting the new family Poliosauridæ, are not far removed from the Permian rhynchocephalians of the suborder Protorosauria; but the other forms display great specialisation, which to a great extent obscures their rhynchocephalian affinities. The great development of the dorsal spines of the vertebræ is the most obvious feature of this specialisation, but it is accompanied by others such as the roofing over of the upper temporal fossa, the mode of rib-attachment, and the enormous size of the claws. Although in earlier stages the spines may have served some useful purpose, in their full development they are regarded by Dr. Case as a mere redundancy of growth, possibly an example of that development of spiny outgrowths and excrescences which appears to mark a decadent group. In addition to North America, pelycosaurs occur in Bohemia (*Naosaurus*), and not improbably in Central Germany and France; but they appear to be unknown in Russia and Africa.

Coming to the anomodont, or theromorphous, group, we find Dr. R. Broom, in the journal already quoted (p. 376), describing a new species of the theriodont genus *Ælurosaurus* from Aliwal North; while in the *Annals* of the Natal Museum (vol. i. p. 168) he makes known a new *Dicynodon* and a new *Scymnosaurus* from that colony. *Scymnosaurus*, which is one of the carnivorous types, appears to be nearly related to *Inostranzevia*, of the Russian Permian. In America, Dr. Case has recently described two nearly complete skulls of the cotylosaurian genus *Bolosaurus*, from the Permian of Texas; the paper forming article 28 of vol. xxxii. of the *Bulletin* of the American Museum.

The relationship of the anomodonts (in the widest sense of that term) to mammals has continued to attract the earnest attention of Dr. Broom, who, in a paper published in the *British and South African Association's Report* for 1907 (vol. iii. p. 12), summarises the evidence in the following words:

"We may regard it as fairly well established that mammals are descended from one of the mammal-like reptiles, and almost certainly from a cynodont (theriodont). The known cynodonts are mostly too large to have been the ancestors, but there is evidence of there having been numbers of small forms, and it was probably from one of these that the new stock arose. And I think we may also safely conclude that all mammals are descended from one common ancestor. By one or two authorities it has been argued that the monotremes are a race apart, and it has even been suggested to remove them from the mammals altogether; but all recent research has confirmed the earlier view that monotremes are typical mammals, and in skeletogenesis are quite as near the marsupials as the marsupials are to the higher forms."

It may be added that Dr. Broom is firmly convinced that *Tritylodon* is a mammal. "As it can be shown," he writes, "from the structure of the molars, that the lower jaw was moved backwards and forwards, as in rodents, it is impossible that the articulation can have been of the theriodont type, and we must conclude that Owen's opinion was correct that *Tritylodon* was a mammal."

The following interesting case of apparent affinity between anomodonts and mammals given by Dr. Broom in the *Zool. Anzeiger* (vol. xxviii. p. 106) may likewise be quoted. It has long been known that in the human subject, and apparently in mammals generally, there exists a remarkable peculiarity in the development of the metacarpal bones of the hand and the metatarsals (or corresponding elements) of the foot. In the metacarpal (or first joint) of the thumb and the metatarsal of the great toe the separate cap, or epiphysis, is situated at the basal extremity, whereas in the other metacarpals and metatarsals it is developed at the opposite end of the bone. The solution of the puzzle has been found by Dr. Broom, who has discovered that in anomodonts the outermost of the second row of bones in the wrist and the ankle is so elongated as almost to resemble a metacarpal or metatarsal. Owing to this elongation, the main joint of the thumb and great toe appears to have been between the wrist or ankle and the metacarpal or metatarsal (as the case may be), while in the other digits this joint was situated between the metacarpal or metatarsal and the first segment of the fingers or toes. Those ends of the bones which took part in the main joint would be the last to ossify, and would determine the points where the caps, or epiphyses, would form. The anomaly in this respect in the human subject seems therefore to be a direct inheritance from reptilian ancestors.

Work on labyrinthodonts (stegcephalians) appears to have been limited. Prof. H. G. Seeley has, however, described in the October number of *The Geological Magazine* a new genus and species from the Karoo series of South Africa under the name of *Ptychosphenodon browni*; and Mr. E. C. Case (*Bull. Amer. Mus. Nat. Hist.*, vol. xxiii. p. 665) has published notes on remains from the Permian of Texas which throw additional light on the structure of the genus *Zatrachys*.

Perhaps the most important contribution to fossil ichthyology is a memoir by Mr. C. R. Eastman on the Devonian fishes of the New York district, published by the New York State Museum. The memoir, in addition to a large mass of descriptive and technical detail, is written from a broad and philosophical standpoint, and contains much information and many suggestions as to the habits, phylogeny, and migrations of these Palæozoic fishes. An interesting generalisation, based upon examples from numerous groups, is that those types of fishes which show no tendency to progressive evolution undergo a kind of degenerative development so as to assume a more or less distinctly eel-like form of body. This is true among the acanthodian sharks, which declined towards the close of the Palæozoic epoch, dying out with the Permian. Their fins, being essentially skin-structures, were incapable of strengthening by bony rods, after the fashion obtaining in other contemporary and competing groups. Hence these fishes, as they became worsted in the struggle for existence, changed their habits and their physical structure. Devonian species, for example, with the graceful fusiform proportions of swift swimmers, became replaced in the Carboniferous by overgrown, unwieldy creatures like *Gyracanthodes*, which were evidently grovellers in the slimy mud of land-locked seas and estuaries; while the expiring Permian forms exhibit a distinct approximation to the eel-like type of body.

Passing southward of the isthmus of Panama, fish-remains from the Cretaceous of Bahia form the subject of a paper by Dr. A. Smith Woodward in *The Quarterly Journal of the Geological Society* (vol. lxiii. p. 131). These indicate a curious mixture of Wealden and middle or upper Cretaceous types; *Lepidotus mawsoni* being, for instance, near akin to the well-known *L. mantelli* of the English Wealden, while *Megalurus mawsoni* appears to be a Jurassic rather than a Cretaceous form of amioid fish. On the other hand, the freshwater herring *Diplomystus longicostatus* is a member of a genus common in the upper Cretaceous of the Lebanon and the lower Tertiaries of Europe and North America. The new genus and species *Mawsonia gigas*, a member of the cœlacanth ganoids, may be either Jurassic or Cretaceous, although more probably the latter.

The same author has contributed to *The Geological Magazine* (decade 5, vol. iv. p. 193) an account of the fossil fish-fauna of Pernambuco, in which the new species *Rhinoptera prisca* is described.

From the Lahontan beds of Nevada have been obtained remains of a stickleback, which is regarded by Mr. O. P. Hay

(*Proc. U.S. Nat. Mus.*, vol. xxxii. p. 271) as a subspecies of the existing freshwater *Gasterosteus williamsoni*, whose range extends from Alaska to California. The interest of the identification lies in the inference that the Lahontan beds are not older than the Pleistocene.

Pycnodont fishes from the Cretaceous of the Lebanon form the subject of a paper by Mr. E. Henmy in the *Centralblatt für Mineralogie* (1907, p. 360); while Mr. Erich Heineke has published in vol. viii. pt. 3 of *Geol. und Pal. Abhandlungen* a detailed account of the ganoids and teleosteans of the Lithographic Limestone of Nusplingen.

Of *Amyzon brevipinne*, a fish hitherto known only by a single specimen from the (probably Oligocene) Amyzon beds of British Columbia, Mr. L. M. Lambe has described, in the *Transactions* of the Royal Society of Canada (vol. xii. p. 151), a second and less incomplete example from the same horizon. The palæoniscid *Myriolepis hibernica*, from the Irish Coal Measures, forms the subject of a note in the *Annals and Magazine of Natural History* for December 1906 (ser. 7, vol. xviii. p. 416).

In the elasmobranch group Prof. E. Fraas (*Neues Jahrb, Mineral.*, 1907, vol. i. p. 1) gives further details of the structure of the rostrum and dentition of *Propristis schweinfurthi*, a sawfish from the Egyptian upper Eocene. In this fish the "saw," which is slender and abruptly truncated at the tip, and attained a length of rather more than two metres, has the same internal structure as in *Pristis*, but carries teeth only in its terminal fourth; these teeth being short and broad-crowned, with sharp fore-and-aft edges, which slightly overlap one another, thus forming a sawing implement of great power and efficiency. Of the well-known selachian genus *Hybodus*, Prof. E. Koken gives further structural details in a memoir of considerable morphological importance published in *Geol. und Pal. Abhandlungen*, vol. ix. pt. 4.

The controversy as to the mutual relationships and general affinities of the more primitive Palæozoic fishes and fish-like creatures is maintained with unabated vigour in several papers by Dr. O. Jaekel and Dr. L. Dollo. The first group of these papers, most of which were published in 1906 (although they were not noticed in the article on the present subject in last year's SCIENCE PROGRESS), deal with the imperfectly known ptyctodonts, as represented by the genera *Ptyctodus*, *Rhynchodus*, *Palæomylus*, and *Rhamphodus*. In the British Museum *Catalogue of Fossil Fishes* the group, of which only three genera were then known, is placed in the chimæroid order of the Holocephali. In a paper on Devonian fishes published in *Sitz.-Ber. Ges. nat. Freunde, Berlin*, for 1906 (p. 77) Dr. Jaekel accepted this arrangement, with certain modifications. Somewhat later Dr. Dollo (*Bull. Soc. Belge Géol.*, vol. xx. p. 133) denied that the ptyctodonts were Holocephali, although not giving his full reasons for the statement. This was in June, 1906, and a month later Dr. Jaekel (*op. cit.*, p. 180) changed his previous opinion, and classed these fishes in the sturgeon group (Chondrostei). During the present year Dr. Dollo has published a paper (*op. cit.*, vol. xxi. p. 1) in which he not only maintains the opinion that the ptyctodonts cannot be classed with the chimæroids, but goes a step further, and definitely places them in the Arthrodira, that is to say with *Coccosteus* and its relatives. He also expresses his opinion that the Holocephali are specialised derivatives from the Palæozoic cochliodont sharks.

In another paper, on the new genus *Pholidosteus* and the mouth-opening and bodily form of the Placodermata, published in the *Sitz.-Ber. Ges. nat. Freunde, Berlin*, 1907 (p. 170), Dr. Jaekel reiterates the views expressed by him in 1902 in regard to this group. Our readers may be reminded that under the title of "Placodermata" the author unites the Ostracodermata (*Pteraspis*, etc.) with the Arthrodira (*Coccosteus*, etc.), although by most authorities the two latter are widely separated. Dr. Jaekel regards all the placoderms as true fishes, which, apart from the retention of certain ancestral features derived from amphibians, are related to the Holocephali (chimæroids), Elasmognathi (sharks and rays), and Chondrostei (sturgeons), with some indications of kinship to the Dipnoi (lung-fishes). These groups he would brigade together under the title of Hypostomata, in contradistinction to the Teleostomata, which include all other fishes.

The list of these primitive fishes has been augmented by Mr. E. Hennig's description, in the *Centralblatt für Mineralogie*, 1907, p. 584, of a new species from the Palæozoic rocks of Gerolstein, referred to the genus *Macropetalichthys* (an ally of *Asterolepis*), with the name *M. pelmensis*.

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THE TRANSFORMATIONS OF ELEMENTS

PART I.—THOSE DETECTED BY RADIOACTIVE METHODS; WITH SOME ACCOUNT OF THE PROPERTIES OF THESE ELEMENTS, SO FAR AS KNOWN

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Section 1.—Methods employed in the Detection of Radioactivity: Thorium and its Products

Radioactive substances are defined as those which possess the property of *spontaneously* emitting *radiations* or *rays* capable of passing through plates of metal, or other substances opaque to light. The word *ray* was first used in a definite sense by Newton, who employed it both in the sense of undulations and of corpuscles, in the latter sense especially in defending the old corpuscular theory of light. The rays, or radiations, emitted from radioactive bodies may be in like manner either corpuscular, or consist of undulations in the ether; both kinds are known. Such radiations possess certain characteristic properties. The most important are their penetrative power, emphasised in the definition, their action on photographic plates, and especially their property of discharging electrified bodies. The second of these properties first led to their detection; the last is the means most commonly employed in their study.

Cathode rays and *Röntgen* or *X-rays* possess such properties. So do the rays emitted under certain conditions by zinc sulphide and similar substances. They are not produced spontaneously, however; the substances producing them are not radioactive.

In 1896 Henri Becquerel found that potassium uranyl sulphate emitted rays which acted on a photographic plate enveloped in black paper, and even separated from the uranium salt by thin plates of metal and other opaque substances. He found later that all the compounds of uranium, and the metal itself, possessed the same property. They not only appeared capable of giving off these radiations continuously, thereby giving rise to a continual supply of energy, but seemed perfectly unchanged by so doing. The action is spontaneous, and uranium is therefore the first element in which the property of radioactivity was discovered.

Uranium salts, besides acting on photographic plates, possess the other radioactive property of discharging electrified bodies. A charged *electroscope* consisting of strips of gold or aluminium leaf suspended from an insulated support, and separated from each other by the repulsion of their electric charge, is usually employed to test materials supposed to be radioactive. Not only is the electricity discharged by radioactive materials, but the rate at which the leaves fall together varies with the degree of radioactivity, other conditions being the same. Different uranium salts discharge an electroscope at different rates; they have different *activities*. Madame Curie has shown that this difference is due, primarily, to the varying proportion of uranium; the radioactivity is proportional to the percentage of uranium in the salt employed. When she extended these quantitative measurements to uranium minerals, this relationship was found to hold no longer. Certain varieties of pitchblende—which consists largely of uranium oxide—were four times as radioactive as the uranium they contained. Chalcolite, copper uranium phosphate, was twice as active; artificial chalcolite gave a figure agreeing with theory. These differences led M. and Mme. Curie to analyse systematically the mineral pitchblende, using the degree of activity as a test for every precipitate, and separating by repeated operations the radioactive from the inactive precipitates. In this way the two elements *polonium* and *radium* were isolated in 1898.

By similar methods during the last eleven years no fewer than twenty-four new elements have been discovered, most of them radioactive. The history of science shows no parallel with the advance made in this subject. It is comparable with half a century's work in other directions of research. The advance is due in great part to the work of Prof. Ernest Rutherford, who has co-ordinated the facts by putting forward, and in part proving, the first reasonable theory to explain the great mass of data which is even yet accumulating.

The electrical measurements of radioactivity are made with some form of electroscope or electrometer. The electroscope devised by C. T. R. Wilson, and used largely for measuring small amounts of activity, may be taken as typical. The description is that in Rutherford's *Radioactivity*, p. 86. A brass cylindrical vessel (or very frequently a tin can) is stoppered at the metal mouthpiece M (fig. 1) by an ebonite cork or an ordinary cork covered with sulphur. Through this passes a metal rod R, supporting a sulphur bead S, which supports and at the same time insulates a narrow brass plate B some two or three inches in length. To the upper end of the brass plate is attached a strip of gold, or better, aluminium, A. The sliding metal rod C C′ is used to charge the leaf system, usually by touching it with a charged rod of sealing-wax while it is in contact with B. R is earth-connected and C revolved to break the

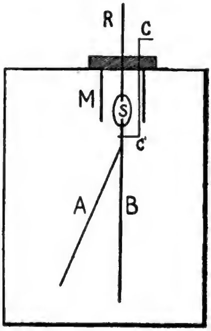


Fig. 1.

contact with the brass and aluminium. The charged aluminium leaf is repelled through a considerable angle. Its movement is observed by a telescope through windows in the brass or tin vessel. The telescope carries a scale; observations are made of the time taken by the falling leaf to traverse a certain fixed portion of that scale. The bottom of the vessel is usually removable, the substances to be tested for radioactivity being thus introduced. In testing gases an airtight apparatus is used and the gases are introduced through metal stopcocks.

Under ordinary conditions, in the absence of radioactive matter the time taken by the falling leaf to pass over the fixed portion of the scale is termed the *natural leak* of the electroscope. This natural leak is quite considerable, and the time may even amount to several hours. The presence inside the case of a comparatively weak radioactive substance reduces the leak to a few minutes, or even seconds. It is desirable to give some account of the reasons underlying this behaviour.

An electroscope can be discharged readily through the action of several different kinds of energy. Thus rays of ultraviolet light allowed to fall on the outer disc of an ordinary electroscope, or the rays given out by a lighted candle placed near it, cause the leaves to fall together rapidly. X-rays behave similarly, and through a detailed study of their behaviour J. J. Thomson and Rutherford have put forward a theory capable of explaining the whole series of phenomena; so far it has stood the test of experience. The different rays are supposed to give rise to particles termed *ions* carrying either positive or negative charges of electricity. The initial action is a collision with an atom of the gas which the ray is traversing; an *electron*, or negative particle of electricity, is set free, the atom minus this electron exhibiting a positive charge. Both, by virtue of their charges, attract to themselves a cluster of uncharged atoms. The number in the case of the electron is estimated at about thirty; the positive cluster is smaller. Both clusters behave like ordinary charged bodies, being attracted by unlike, repelled by like, charges of electricity. Consequently in the absence of any strong electric charge in their neighbourhood they ultimately collide with each other, and their charges become neutralised. But if such ions are liberated in the neighbourhood of a charged electroscope, it will attract ions with unlike charge in sufficient number to discharge itself (since the charge on the electroscope is likewise due to the presence of free electrons, if negative, or to free positive ions).

It is found that ordinary air always contains a certain very small number of ions, and the natural leak of an electroscope is due to their presence. Again, the production of ions is strictly proportional to the number of rays—*e.g.* if two quantities of uranium oxide are taken, one twice the weight of the other, and they are spread out in thin films of the same thickness, so that the first has twice the exposed area of the second, it will emit twice as many rays as the second; they will produce twice the number of ions, having twice the effect on the leaves of an electroscope; hence it will be discharged in half the time. Similarly if equal quantities of two radioactive materials are taken, and consecutively introduced inside an electroscope, and it is found that the rate of discharge of the first is twice as fast as that of the second, then it is said to possess twice the activity of the second. The measure of the discharge-time gives a measure of the radioactivity. By comparing the effect produced by a substance from day to day, a measure of the variation in its radioactivity is obtained.

The most convenient instrument for these measurements, however, is some form of quadrant *electrometer*, preferably the modification invented by Dolezalek in 1901. This has a very light needle of silvered paper, carrying a small mirror, and suspended by a very fine quartz fibre between the four quadrants. One pair is connected to earth, the other to an insulated metallic plate, facing a second which carries the radioactive matter to be tested. Through action similar to that in the case of an electroscope an electric stress is set up between the two pairs. The needle, previously charged to a very high potential, is repelled from one pair of electrodes towards the other; on account of its extreme lightness it moves at a uniform rate. The time taken to pass two fixed points is observed by means of a stop-watch. As in the case of an electroscope, this time is inversely proportional, other conditions being the same, to the degree of radioactivity of the deposit under observation. The natural leak of the electrometer is deducted from all other time measurements. The electrometer is standardised from time to time against a definite amount of uranium oxide, which is known to give a constant supply of radiation. In this way any variations in the instrument are corrected.

The photographic action of the radiations has been largely used in certain branches of the subject, but does not give good quantitative results. The method employed is the exposure of the photographic plate wrapped in black paper—to cut off phosphorescent light—to the effect of the radiations. The time of exposure varies from a few minutes, with almost pure radium preparations, to perhaps seventy-two hours, with very weak radioactive preparations. With long exposures the results are especially untrustworthy on account of the difficulties experienced through the plates fogging.

In order to show how the instruments are actually employed and deductions made, a brief account will be given of the results obtained to the present time from the study of **thorium** compounds. The greater part is taken from Rutherford's *Radioactivity*, second edition.

Schmidt and Madame Curie independently discovered the radioactivity of thorium compounds in 1898. Four years later Rutherford and Soddy found that the thorium hydroxide precipitated by ammonia from a solution of the nitrate was less than half as active as the original solid salt; the filtrate on evaporation gave a residue which, weight for weight, was several thousand times more active. They named this active residue **thorium** X (ex-thorio). It consisted largely of impurities existing in the original nitrate; the true thorium X was present only in minute quantity, and could not be separated. It became inactive at the end of a month; in the same time the thorium completely regained its activity. They concluded therefore that thorium X was actually produced from thorium. They proceeded to study the time-rates of these processes, making electrical measurements at intervals over a long time. Their results are shown in fig. 2, A (*Radioactivity*, p. 221); the curves are typical of most of those illustrating the decay and production of radioactive matter. The initial activity of thorium X was arbitrarily taken as 100; similarly that figure was taken for the final activity of the thorium compound. The activities were expressed along the ordinates, the times from the initial measurement along the abscissæ. The initial irregularities in the curves were due to the presence in the original thorium compound of further disintegration products of thorium X; these are also radioactive, and produce their own electrical effect. They were precipitated with the thorium hydroxide. The initial part of the *recovery curve* is due to their activity rapidly becoming smaller as they themselves disintegrate—more rapidly than is counteracted by the gradual reproduction of thorium X. The initial part of the *decay curve* is due to their reproduction from thorium X, when their activity gives an added effect to the activity of thorium X itself. In both cases a time is reached when in any given interval, say a minute, as much of these substances is produced as decays in that same time. These products are then said to be in *radioactive equilibrium*, and no longer affect the nature of the curve. The times in question are represented by the minimum and maximum on the respective curves, and it will be noticed that these exactly correspond. If the true curves are then continued back till they meet the axis, and the maximum values in both cases again taken as 100, the corrected values are shown in fig. 2, B (*Radioactivity*, p. 222). The decay curve is *logarithmic*, that is to say, if the logarithms of the activity values are plotted against time (instead of the true activity values), the result is always a straight line. This is shown in the figure. Such

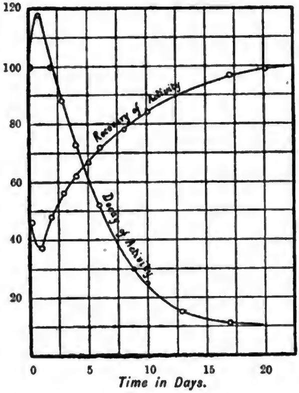


FIG. 2 A.

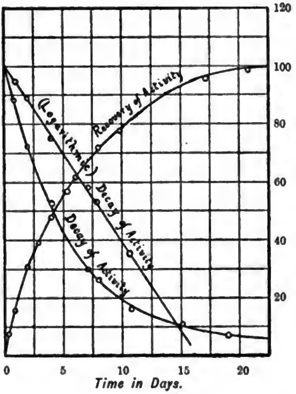


FIG. 2 B.

logarithmic or *exponential* curves correspond to an equation of the type—

$$\frac{I_o}{I_t} = e^{-\lambda t} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1).$$

In the case under consideration I_o is the initial activity of thorium X, I_t the activity after time t, λ is a constant, and e the natural base of logarithms (= 2·7183 ...).

The recovery curve is the inverse of this curve, and is represented by the equation—

$$\frac{I_t}{I_o} = 1 - e^{-\lambda t} \quad . \quad . \quad . \quad . \quad . \quad (2),$$

where I_o is the final activity (the maximum figure obtained), I_t the activity recovered after time t, and λ is the *same constant* as in the previous equation.

These results have been given in some detail because they are typical of most of the curves obtained by plotting the change of activity against time. In all cases the decay curve of the *radioactive child* bears the relation to its *radioactive parent* that the constant λ is the same for the two cases. The curves illustrate two further points. They approach constant value towards the end of a month, but it is seen that they reach a final value only at infinite time. This property is common to all such curves; it illustrates the fact that the *life* of a radioactive element is infinite. In order to compare such lives we therefore speak of the *half-life period*, a definite value for each element. It represents the time in which half the element disintegrates; its activity falls to half value. This time can be calculated graphically from the curves, or from equation (1), since the activity has fallen to half value, $I_o = 2I_t$, *i.e.* $2 = e^{-\lambda t}$. Hence if λ is known, t can be calculated. Again, λ represents the proportion of atoms changing per unit of time; $^1/\lambda$ thus represents the *average life* of an atom of the element under consideration. A discussion of the meaning of these terms is given in Section 3 (p. 538). In the case of thorium X the half-time is four days.

Hahn has recently shown that thorium at first disintegrates into **mesothorium**, and this into **radiothorium**; the last named is the immediate parent of thorium X. Radiothorium is very much more active than the thorium from which it is derived. The methods employed were similar to those just described—

chemical separations, followed by measurement of the radioactivities of the different products.

Early workers on thorium noticed that the amount of radiation given off was subject to variation. Owens, in 1899, traced this inconstancy to air-currents passing over the surface of the thorium. Rutherford, next year, showed that it was due actually to a gas—hence the effect of air-currents. It could be drawn through tubes along with a current of air, passed through cotton-wool, bubbled through solutions, and gave thereafter an electrical effect. It thus behaved in every way like a true gas, although it could not be isolated, and could only be tested by its radioactive properties. Rutherford termed it an **emanation.** It has a very short-life period. Its decay was studied by drawing it into a cylinder by an air-current, closing the cylinder, and noting the radioactivity from time to time by the electrical method (the cylinder containing insulated metallic discs connected to an electrometer). Its half-life period is 54 seconds.

This emanation of course disintegrates into something else. When some quantity of it is allowed to decay in any closed vessel, the products are deposited on the walls of the vessel. They themselves give off radiations; the phenomenon is known as *excited* or *induced activity*, the deposit as the *active deposit.* It differs in chemical and physical properties from all its predecessors. The emanation can be washed out with air, and the decay rate of the deposit studied. The curve is complex; mathematical analysis indicates at least two products. These were postulated as **thorium A** and **B**. They were differentiated more clearly by the work of Miss Slater, who studied the effect of temperature on them. A platinum wire was exposed for a considerable time to the action of the emanation, whereby (relatively) a considerable amount of the after-products was deposited on it. It was then heated by an electric current. A lead cylinder surrounding it caught any volatilised matter. Both wire and cylinder were then tested separately by an electrometer, the decay of the radioactivity being studied. Heated to about 700° C. the amount of radioactivity on the wire remained constant, but the decay rate was faster than usual. The cylinder was at first only very slightly active, but the activity grew rapidly, the maximum being reached in four hours; the decay rate thereafter was normal. These phenomena were easily explained by the hypothesis that thorium A, the first product, volatilised below 700° and was *inactive—i.e.* gave no radiations; the thorium B, already produced from it, remained on the wire unvolatilised at 700°, and a fresh amount was slowly produced on the lead cylinder. Further work has slightly modified this result, thorium A being found to have a very slight radiation, and there being two later products, thorium B and C, all three having an extremely short-life period. The final product is inactive. So far as present knowledge indicates, the whole series is:

Thorium → mesothorium → radiothorium → thorium X → thorium emanation → thorium A → thorium B → thorium C → inactive product.

Most of the above work has been accomplished by what may be described as the *direct method* of work. In addition an indirect method, based on chemical means, is frequently employed. It will be discussed more particularly in the subsequent parts of this paper. An example will be mentioned here.

The final product of the uranium-radium disintegrations is supposed to be lead, another product being helium. Boltwood has analysed a great number of uranium minerals; they all contain lead. He finds that the ratio, amount of uranium to amount of lead, varies with the age of the mineral, the older rocks giving a higher percentage of lead. This agrees with the theory that lead is slowly produced from the uranium and radium. Strutt has analysed thorium minerals for helium; he finds evidence of some definite relationship between the quantities of thorium and helium which they contain.

SECTION 2.—NATURE AND PROPERTIES OF THE RADIATIONS FROM RADIOACTIVE ELEMENTS

When an electric current is passed through a highly exhausted vacuum tube, three kinds of rays are produced in it. If the cathode is perforated, *canal rays*—so named by Wien—are projected with enormous velocity in the direction opposite to that in which the current is travelling; they consist of particles, each at least as heavy as a hydrogen atom, and always carry a positive charge of electricity. *Cathode rays*, consisting of negative particles of electricity, convey the current from cathode to anode, while *Röntgen rays*, undulations in the ether, are projected in all directions. To these three kinds of ray correspond the three radiations which are emitted by radioactive matter. Like the canal rays are the *α rays*, heavy particles carrying a positive charge; the *β rays* are electrons like the cathode rays; while the γ rays strongly resemble Röntgen rays.

They are frequently emitted simultaneously from active preparations. Two properties allow of their study and differentiation: :

(1) They behave differently under the action of a magnetic field;

(2) Different kinds of rays penetrate matter to very different degrees.

Under ordinary conditions all these rays, like light rays, travel in straight lines. Under the action of a very strong magnetic field the path of the α rays becomes slightly curved; β rays are much more easily deflected, and, moreover, in the opposite direction to α rays—compare the fact that α rays carry a positive charge, β rays a negative one; γ rays are not deflected by a magnetic field.

The difference in penetrating power is well shown by the following table (Rutherford, *Radioactivity*, p. 111):

Radiation.	Thickness of Aluminium in cms., which cuts off half the radiation.	Relative power of penetration.
α-rays	0·0005 cms.	1
β ,,	0·05 ,,	100
γ ,,	8 ,,	10000

These ratios are only approximate; rays from different material have greatly varying penetrative power. Different substances absorb them in widely different amounts; the density of the substance is a factor in determining the amount of absorption.

The radiations—as has been pointed out in Section 1—produce ions in the gases they traverse; the mechanism is collision. Their ionising power varies very greatly, being roughly the inverse of their penetrability.

The enormously greater ionising power of the α rays supports the theory that they are heavy particles shot off from the disintegrating atoms at enormous velocities. Such large particles cannot travel far without colliding with gas particles, hence their small penetrative power. Their enormous momentum produces the correspondingly great ionising effect actually observed. Rutherford has measured the velocity of α particles from different active elements; it varies from $1{\cdot}56 \times 10^9$ cms. per second in the case of radium to $2{\cdot}25 \times 10^9$ cms. per second for thorium C. Light travels at about 30×10^9 cms. per second. The experiments lead to the conclusion that the substances possessing longest life, viz. uranium and radium, emit particles having the least velocity; the shorter the life the greater the velocity of the emitted α ray. Rutherford has been able to measure the mass of the particle which carries unit charge of electricity; it is about twice that of hydrogen. From this he concludes that the α particle consists either of a half atom of helium (atomic weight 4) carrying one electric charge, or a whole atom carrying a double charge. The α rays carry a positive charge—their mass and velocity correspond very closely with those of canal rays; their close resemblance to these must be held as established.

The β rays have a greater range of velocity. The maximum velocity approximates to that of light (200,000 miles per second). Their identity with cathode rays has been established on three grounds: (*a*) the negative electric charge carried by both; (*b*) the ratio of that charge to the mass—extremely small in both cases—which carries it; and (*c*) the fact that a magnetic field has precisely the same effect in both cases.

α and β rays are completely absorbed by covering the radioactive matter producing them with a layer of lead 1 cm. in thickness. But even if a layer of 1 inch is used, rays still pass through. They carry no charge of electricity, and are not deflected by a magnetic field, yet they ionise gases, and so affect an electrometer. These are the γ rays, ether waves, corresponding to X-rays, but of even greater penetrating power.

All three kinds of rays on impinging on solid particles give rise to *secondary rays*, as do ordinary X-rays. The secondary rays also travel in straight lines, and otherwise obey the light laws, but are deflected by a magnetic field. They resemble cathode rays in being electrons, but move with comparatively small velocity. Ultra-violet light allowed to fall on the surface of metals produces a similar phenomenon.

In examining a radioactive substance to find what kind of radiations it gives rise to, the method in use is to cover it with varying thicknesses of aluminium. Absorption takes place to different extents; the ionisation varies accordingly; this is recorded by electric measurements. From a study of results thus obtained it can usually be determined whether one or more kinds of ray are present; the results are confirmed by noting the action of a magnetic field on rays which have penetrated the different thicknesses of metal.

The radiations produce a considerable number of effects—physical, chemical, and physiological. One of the most important is the phosphorescence induced in many substances subjected to bombardment by the rays. Zinc sulphide, a particularly good example, is rendered luminous by both α and β rays. Crystals of the different platinocyanides give different colour effects according to their composition. The lithium salt phosphoresces pink, the calcium and barium salts deep green, the sodium salt yellow. Willemite, a zinc silicate, becomes beautifully green in colour and apparently translucent. Kunzite shows a red phosphorescence under the action of β and γ rays; α rays are without effect on it. All strongly radioactive compounds phosphoresce strongly themselves.

The diamond not only phosphoresces when bombarded by radium rays, it also changes colour. Sir William Crookes found that a yellow diamond, after seventy-eight days' exposure to the rays, became bluish green. Prof. Bordas has recently experimented with uncoloured rubies; after some weeks' exposure they became dark brown, and in some cases pink; sapphires similarly change colour. The effect is in all these cases probably due to the action of β rays, and is analogous to their action on different glasses. Soda glass is coloured deep violet, potash glass a dark brown, gold glass ruby colour. Similar effects are produced by cathode rays in vacuum tubes. The colour is discharged quite easily by heating the glass to 300–400° C. Maxwell Garnett has made a detailed study of these phenomena, and his work supports the hypothesis that metallic ions are actually liberated in the glass, and that the colour is due to these, violet for sodium, brown for potassium, and so on; application of heat causes recombination with accompanying loss of colour. It should also be mentioned that glass tubes containing radium emanation show a beautiful green phosphorescence. Under similar conditions quartz glass shows a fine electric blue colour.

The rays change oxygen into ozone. Hence all dry radium salts smell strongly of ozone. In water this effect is not produced, hydrogen peroxide being formed instead. Radium salts and its emanation decompose water. The emanation also effects the recombination of hydrogen and oxygen. These phenomena are in all probability produced by the α rays.

Under the action of β rays yellow phosphorus is converted into the red variety, while iodine is liberated in iodoform solutions. Much work yet remains to be done in this branch of the subject.

Radium rays, like X-rays, produce painful burns. Painful irritation is caused, then inflammation lasting from ten to twenty days. The skin finally peels off. The physiological effects of radium emanation have been tried on mice and guinea-pigs. Long exposure to such treatment is in most cases harmful, in some fatal. Radium rays have a beneficial result in the case of ulcerous growths, but do not cure true cancer. Their effects are thus similar to those of X-rays, but they have the advantage that the radium preparation, enclosed in a small tube, can be applied locally. The medicinal effects of many natural waters are supposed to be due to the presence of small quantities of radium emanation. They are slightly radioactive. Artificial waters of exactly the same chemical composition do not possess the same beneficial effect.

SECTION 3.—LIFE OF A RADIOACTIVE ELEMENT

A typical radioactive element gives rise continually to a radioactive product, together with one or more kinds of rays; radium gives rise to its emanation, and to α rays. In addition, heat in comparatively large quantity is continually liberated.

This continuous production of both energy and matter is explained by Rutherford by the assumption that atoms of the parent element are continually being broken down, or disintegrated, into simpler atoms, the heat and rays being the difference in energy-content in the two atomic systems. When guncotton is exploded a complex molecule is broken up into simpler ones, heat and light being also emitted. The two cases are parallel, the one being atomic, the other molecular.

It is found that the emanations, and many other active products, lose their activity almost completely in a measurable time. From studies of the rate at which the activity is lost, the conclusion is reached that in any one time a certain fixed proportion of the total number of atoms present spontaneously disintegrates. An actual illustration will make this clearer. The activity of any fixed quantity of radium emanation falls to half the initial value in approximately four days. In the second four days it falls to half of this second value, *i.e.* one quarter of the original. We therefore suppose that the emanation has decomposed to a corresponding extent. In the unit of time chosen, four days, the same quantity, one-half the amount at the beginning of that period, always disappears. Similarly in any other definite period of time a certain quantity, bearing a definite ratio to the original amount, will disappear. Again, at the end of eight days one quarter of the whole amount remains; at the end of twelve days, one-eighth; of sixteen days, one-sixteenth. But at the end of infinite time there will always remain some quantity, however small. Similarly in all cases of active matter some remains undisintegrated after infinite time; the radioactive elements have an *infinite life*. Though they may have *died* for all practical purposes at the end of some measurable time, an unmeasurable but definite amount remains. However, it has been shown in Section 1 (p. 532) that we can always find when half a given quantity of active substance has disappeared. And it is this period which is termed the *half-life period* of such substances. It varies from four seconds in the case of actinium emanation to millions of years in the case of uranium.

Another term constantly used is the *average life* of a substance. In Section 1 the method of calculating it has been given (p. 532). It can be conveniently illustrated by a human parallel. A church filled with people on any fixed date contains a fair assortment of men, women, and children of all ages. If we know the total number of years each person will live after leaving that church we can calculate the *average life* of the congregation counting from the definite time fixed by that church attendance. This is quite different from the *average life* of some number of persons from the time of birth of each, which is the basis of the data employed to calculate insurance rates.

The *average life* of a radioactive element at any definite time corresponds to the first of these illustrations. If we take a definite quantity of radium salt, then the atoms of radium it contains are of all ages. If they have just previously been separated from their uranium ore some may have been *born* only a few weeks previously, others have existed thousands of years, just as the church congregation may include infants and old men of ninety. Of the radium atoms a certain number will *expire* in a definite time, just as in so many years a number of the worshippers will have died. And we can calculate the average life of the congregation of atoms with as much certainty as that of people.

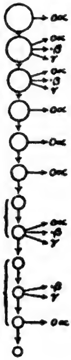
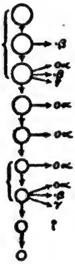
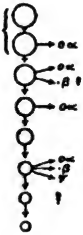
The application of the second kind of *average life* to radioactive substances was recently worked out in some detail by Sir William Ramsay as a lecture illustration. Though it has just been stated that the life of a radioactive atom is infinite, yet infinity is only a relative term; in this connection it only means a longer time than we can measure. It is extremely probable that just as the human life is measurable and definite, so is, let us say, the life of an atom of radium. One may go further. For there is much more regularity in the life of this dead matter; the life of human beings is variable, dependent on "all the ills that flesh is heir to," microbes, the bearers of disease, and accidents, the ills of fortune. We have no ground to suppose that the life of a radioactive atom varies from any similar cause. For example, the rate of decay—the death-rate—of radium emanation is unaltered within the limits of measurement between the temperatures of $-180°$ and $+1600°$ C. ($90-1870°$ in the absolute scale), the extremes at which, so far, it has been experimentally tested. If this tremendous difference of temperature does not hasten the decay of a single atom of emanation we can at least postulate that its life is not easily influenced by external causes. So far experimental work has shown that we cannot hasten or retard the death of a radioactive atom; consequently we cannot alter its life. For its birth is but the death of its parent atom, to which the preceding statement likewise applies. And we are justified in stating that the average life of a radioactive atom, as used in the second sense above, is in all probability the actual life of that atom.

SECTION 4.—RADIOACTIVE ELEMENTS AND THEIR PROPERTIES

No fewer than twenty-four new elements have been discovered by radioactive methods; uranium and thorium were known long before their activity was observed. Of these twenty-six elements, five are said to be *rayless*; in them no activity has been detected by the instruments in use at present. The others emit one or more kinds of ray; nine or ten give α particles alone. An appreciable life-period is possessed by nine only—uranium, thorium, radium, polonium, radio-lead, mesothorium and radiothorium, actinium, and probably ionium. The remainder are none the less true elements, although their short life may never permit them to be examined by other than radioactive means.

If the recent work of Boltwood is correct, and ionium is the true intermediate product between uranium X and radium, these twenty-six elements fall naturally into three large groups, namely, the elements uranium, thorium, and actinium, and their respective disintegration products. Using Rutherford's method of classification (from *Radioactivity*, pp. 449-50) in a slightly modified form, the elements can be grouped as shown below. Only the atomic weights of three—uranium, radium, and thorium—are known with any certainty. If the α particle is a helium atom (of atomic weight 4), then the atomic weights of the other elements, calculated by deducting 4 for each α particle evolved, may approximate to those given in brackets. The present state of our knowledge does not allow any stress to be placed on this hypothesis. In the table on the next page Ur = uranium, Th = thorium, Ra = radium, Act = actinium.

The nomenclature of the elements is due to Rutherford; his original idea was to name the first derivatives so as to show their parentage; hence Ur X, Th X, Act X (ex-uranio, ex-thorio, ex-actinio). The discovery of radiothorium and radioactinium upset this system. It will be observed that each group contains one gas or emanation; the elements derived from it are named in order of formation A, B, C, and so on. The graphic representation in the last column, due to Rutherford, illustrates the method of disintegration, the atomic contractions due to loss of α particles being considerably exaggerated in order to emphasise the theory. The brackets show those elements which differ in mass content by not more than one electron.

ELEMENT.	ATOMIC WEIGHT.	HALF-LIFE PERIOD.	NATURE OF EMITTED RAYS.	EXAGGERATED GRAPHIC REPRESENTATION
First Group:				
Ur	238·5	—	α	
Ur X	(234·5)	22 days	αβγ	
Ionium	(230·5)	—	αβγ	
Ra	226·5	1300 years or 164 „	α	
Emanation	(222·5)	3·8 days	α	
Ra A	(218·5)	3 minutes	α	
Ra B	(214·5)	21 „	rayless	
Ra C	(214·5)	28 „	αβγ	
Ra D	(210·5)	40 years	rayless	
Ra E	(210·5)	6 days	βγ	
Ra F	(210·5)	143 „	α	
Inactive Product	(206·5) Cp. lead = 207	—	rayless	
Second Group:				
Th	232·5	—	rayless	
Mesothorium	(232·5)	5·5 years	β	
Radiothorium	(232·5)	737 days	αβγ	
Th X	(228·5)	4 „	α	
Emanation	(224·5)	53 seconds	α	
Th A	(220·5)	11 hours	slow β	
Th B	(220·5)	55 minutes	αβγ	
Th C	(216·5)			
Inactive Product	(?)		rayless	
Third Group:				
Act	?	—	rayless	
Radioactinium		19·5 days	α	
Act X		10·2 „	α (β?)	
Emanation		3·9 seconds	α	
Act A		36 minutes	rayless	
Act B		2·15 „	αβγ	
Act C		?		
Inactive Product		—	rayless	

A short account of the individual elements will now be given, in the order shown opposite.

Uranium was discovered by Klaproth in the mineral pitchblende in 1789. It is of comparatively rare occurrence, and widely scattered. The composition of uranium minerals varies largely; many are complex silicates, phosphates, or arsenates. Pitchblende and uraninite consist largely of uranium oxide, and contain from 50–80 per cent. uranium. The metal was isolated by Peligot in 1842 by the action of potassium on the fused oxide. Thus formed it is a black powder. In the ordinary metallic state it closely resembles iron and nickel. Heated to redness it burns brilliantly. It dissolves in dilute acids, with evolution of hydrogen; combines directly with chlorine, and, on heating, with sulphur. Its atomic weight is 238·5; it is thus the heaviest metal yet isolated. A great number of its compounds have been prepared. The discovery of radioactivity by Becquerel, in 1896, was made with these compounds; it has been shown that the metal is also radioactive. The life of uranium is extremely great. Its half period is many millions of years.

In 1900 Sir William Crookes showed that when excess of ammonium carbonate is added to a uranium solution, until the uranium precipitate has all redissolved, a light cloudy precipitate remains: this contains all the photographic activity; the separated uranium is without effect on a photographic plate (α rays do not affect a photographic plate; uranium gives off α rays only); Crookes called the new product **uranium X**. The precipitate consists largely of impurities from the uranium salt, and insufficient uranium X has been obtained to give a distinctive spectrum. A mixture of ether and water effects a partial separation. The ether layer contains most of the photographic or β-ray activity. Becquerel effected a separation by adding barium chloride and precipitating the barium as sulphate; uranium X is carried down along with it. Recently (in 1906) Moore and Schlundt have described further methods of separation. When crystallised uranium nitrate is dissolved in acetone, or several similar organic solvents, the slight precipitate which remains contains most of the uranium X. Complete separation is effected by adding moist ferric hydroxide to such a solution; the hydroxide carries down all the active matter. Moore and Schlundt state that uranium X gives both α and β rays; 34 per cent. of the activity is due to the α-rays. Levin in 1907 obtained the figure 8 per cent.; in a later paper he states that no *a* rays are produced, the mistake arising from the presence of *β* rays of small velocity. The question has not yet been decided. Uranium X has a half-life period of twenty-two days. In less than a year it has disintegrated almost completely. Into what has it changed?

Ever since Madame Curie succeeded in obtaining radium from uranium minerals, and the theory of disintegration was put forward, it has been considered highly probable that radium is a *descendant*, in perhaps the third or fourth generation, of uranium itself. Some experiments of Soddy in 1904 gave the first proof of this statement. He took about two pounds of uranium nitrate, dissolved it in water, and repeatedly added barium solution, precipitating the barium as sulphate. In this way the solution was practically freed from radium, which is precipitated along with the barium sulphate. In 567 days the solution contained more than one hundred times as much radium as it did immediately after this treatment. This radium was identified by the decay rate of its emanation. The actual amount of radium observed was only one-thousandth of what it should be on the assumption that uranium X was the parent of radium. Soddy postulated one or two intermediate products. Boltwood criticised his method of procedure but afterwards confirmed his results. In 1906 he suggested that the intermediate product was actinium. Soddy and Mackenzie, and also Rutherford, showed that this was impossible, pure uranium nitrate neither giving rise to actinium nor its emanation. Rutherford separated the actinium from solutions of commercial uranium nitrate, and by passing ammonia and sulphuretted hydrogen gases through the actinium solution, he effected the separation of a new radioactive substance, which he considered to be the actual intermediate product between uranium X and radium. Boltwood confirmed this result. He found this new element emits *a* rays (actinium is rayless) which are very easily absorbed, and *β* rays of small penetrability. The activity is of the same order as that of radium. He suggested the name **Ionium**. Hahn has confirmed his conclusion by a different method.

Radium was discovered by Madame Curie in 1898. Her method of procedure has been indicated. Thoroughly examining the different group precipitates in an analysis of pitchblende, she found that the barium group precipitate was strongly active.

This activity could be completely separated along with barium sulphate. Final separation was effected by recrystallising the barium as chloride ; radium chloride is slightly less soluble and separates in the first fraction. In this way crystals were finally obtained nearly two million times as active as uranium. The activity was too great for comparative measurements; the final fractions were tested for purity by estimating the amount of barium spectroscopically.

Giesel showed later that the separation could be effected more conveniently by recrystallising the bromides; the difference in their solubilities is greater than in those of the chlorides.

Radium continually gives rise to a gas, the **Emanation from Radium,** discovered by Dorn in 1900, and no intermediate product has yet been detected. A full account of the properties of radium and its emanation will be given in Part II. of this paper.

When any substance is exposed to the action of the emanation it becames coated with an intensely active deposit. This was first observed by M. and Mme. Curie in 1899. It is known as the **active deposit of rapid change,** and has been found to consist of three consecutive products, **Radium A, B, and C.** The whole activity decays to half value in 28 minutes, but the decay curve is very irregular. Studies of the rates of decay of the different rays led to the analysis into three separate elements. All three are soluble in strong acids, and volatile at a white heat. B is volatile at the lowest temperature, and can be thus partially separated.

In 1903 the Curies also observed that substances which have been covered with this active deposit do not lose all their activity after even a prolonged period. Giesel confirmed this. Rutherford found that the activity increases during several years. It is due to the **active deposit of slow change,** which has been resolved similarly into three consecutive products, **Radium D, E, and F.**

Radio-lead (or Radium D) was obtained by Hofmann and Strauss in 1901. The lead obtained from pitchblende was strongly and permanently radioactive—hence the name radio-lead. In 1904 Hofmann and co-workers showed that the lead itself is not radioactive, but gives rise to active products separable by chemical means; the inactive lead slowly regains activity. It therefore contains an inactive element which disintegrates slowly into active products. Rutherford has proved fairly conclusively the identity of the rayless parent, the true radio-lead, with radium D, and of the active products with E and F. He found that the activity of the short-life deposit from radium practically vanished after two days; thereafter there was a slow increase during eighteen months. The new activity was due to both α and β particles. Two experiments showed the nature of the changes. A deposit on a platinum wire, after standing for some considerable time, was subjected to the action of heat. Below 1000° it was unaffected. Between 1000° and 1050° some part volatilised. It no longer gave off α particles, while the β-ray activity decreased rapidly, falling to half value in six days. During the same time α rays were emitted in slowly increasing amounts.

Clean surfaces of metallic bismuth placed for some time in solutions of the slow-change deposit removed 90 per cent. of the substance emitting α particles. The bismuth thereafter emitted these α particles, activity decreasing somewhat slowly; the half-life period was 143 days. The β-ray activity of the solution remained unaltered by this treatment; after the bismuth was taken from the solution the latter commenced slowly to emit α rays.

A simple explanation is given by the assumption of three elements: radium D (rayless); E, giving β rays only; and F, giving α rays only. D is volatile below 1050°; E does not volatilise at that temperature. D is the parent of E, for after it has volatilised the amount of E rapidly becomes less. F volatilises at 1050°, for the wire loses its α activity. It is produced from E, for the α activity of the wire is slowly regained. F, alone of the three, is deposited on bismuth from solutions, and it is the element whose half-life period is 143 days.

Meyer and Schweidler consider that this hypothesis does not completely satisfy the peculiarities of the curve of decay. They suggest a further intermediate product (thus RaE_1 and RaE_2).

Rutherford has shown the identity of **polonium, radio-tellurium,** and **radium F**. Polonium was the first radioactive substance discovered by Madame Curie. The sulphide precipitate from acid solutions of pitchblende contained an active substance, which associated itself with bismuth. With this element its properties are so closely allied that it is impossible to effect a complete separation. Madame Curie repeatedly precipitated the nitric-acid solution by water. The precipitate contains most of the active material. Marckwald obtained the same substance by dipping a rod of bismuth or antimony in the active solution. These formed an intensely black deposit, chiefly tellurium, and very active; he named the active matter radio-tellurium. Dissolved in hydrochloric acid, all the tellurium was precipitated by hydrazine hydrochloride; the active matter remained in solution. By repeating the process, Marckwald obtained a few milligrams of intensely active material.

There remains the question of the final product. Radium F decays at a moderately rapid rate. What becomes of it? Two lines of argument point to the conclusion that **lead** is formed. On the assumption that the α particle is helium of atomic weight 4, then, since α particles are given out by radium and four of its products, the atomic weight of the final product should be $226{\cdot}5 - (5 \times 4) = 206{\cdot}5$. Lead has the atomic weight 207, a very close agreement.

Again, Boltwood has shown that lead is present in all uranium-radium minerals, and the amount is greatest in the oldest—*i.e.* those in which the greatest quantity of uranium has disintegrated. This also points to the fact that the lead is derived from uranium, and therefore from radium.

Thorium was discovered by Berzelius in 1828. It occurs chiefly in Ceylon, the recently discovered mineral thorianite containing more than 70 per cent. of it. It is precipitated from solution by ammonia, and usually separated in the form of oxalate. The metal has been prepared as a grey powder; it burns brilliantly in air, and is easily dissolved by warm, dilute acids. The oxide ThO_2 is usually obtained by calcining the oxalate or sulphate. A large number of the salts have been prepared.

An account of the disintegration changes of thorium has been given in Section 1 (pp. 530-534). It need only be mentioned here that the emanation is an inert gas strongly resembling the gases of the argon group, while the activity of radiothorium is several hundred thousand times that of thorium itself. Rutherford suggests that the final disintegration product of thorium may possibly be bismuth.

Actinium was discovered by Debierne in 1899, and independently as *emanium* by Giesel in 1902; it is precipitated with the group of cerium earths, and is closely allied to lanthanum. It is many thousand times more active than thorium; although it strongly resembles that element, yet all the products of the two have entirely different decay rates—a sufficient proof of their separate identities.

Hahn, in 1907, succeeded in showing that actinium is rayless, its activity being due to its first product **radio-actinium**; this gives α rays only, corresponding to radiothorium. According to Giesel it resembles the alkaline earth metals, and can be precipitated from actinium solution by means of finely divided sulphur. It disintegrates into **actinium X**, independently discovered in 1905 by Giesel and Godlewski; the separation is similar to that employed for thorium X. The emanation was observed by both Debierne and Giesel; Godlewski proved that actinium X was its immediate parent. Debierne has recently noted the production of helium from this emanation; Giesel has confirmed the statement. The analysis of the active deposit from the emanation is in great part the work of Miss Brooks. Her work led to the recognition of **actinium A** and **B**; Meyer and Schweidler consider that **C** and **D** also exist.

So far we have no clue to the atomic weight of actinium. But it corresponds to lanthanum; in that case it either comes between radium and thorium, with an atomic weight of about 230, or has a greater weight than uranium. Actinium emanation most probably belongs to the argon series, in the periodic system, when it follows that radio-actinium corresponds to radium (it resembles the alkaline earth metals) and actinium X occupies the space below gold. With similar treatment of the thorium products we can postulate some such arrangement as the following for the higher members of the periodic system; it accepts the simplest hypothesis of disintegration—that it is accompanied by loss of mass.

Kr 87·8	Rb 85·4	Sr 87·6	T 89	Zr 90·6	Cb 94	Mo 96	...	Ru 101, Rh 103, Pd 106·5
...	Ag 108	Cd 112·4	In 115	Sn 119	Sb 120	Te 127·6	I 127	...
X 128	Cs 133	Ba 137·4	La 139	Ce, etc., 140-178	Ta 183	W 184	...	Os 191, Ir 193, Pt 195
...	Au 197	Hg 200	Tl 204	Pb 207	← RaF ← Bi 208·5	(?RaE) ←	(??RaD) ← ? ← ? ←	(RaC) ← (RaB) ← (RaA) ← (ThC) ← (ThB) ← (ThA) ← (ActC) ← (ActB) ← (ActA) ←
Ra Em Th Em ← Act Em ←	← Th X ← Act X ←	Ra 226·5 Radioth ← Radioact ←	← Mesoth ← Act	Ionium ← Th 232·5	UrX ←	U 238·5		

There are several difficulties in the way of accepting such a scheme. For example, radium D has given no indications of any resemblance to the halogens; on the contrary it strongly resembes lead. Although such hypotheses must therefore be put forward very tentatively, we can scarcely evade the conclusion that many higher members of the series have almost coincident atomic weights, while there are several cases of at least two elements occupying one space in the table. Thus, considering the radium and thorium products alone, their emanations are both inert gases strongly resembling the argon gases. To move one a space higher in the series, the difference in their atomic weights must be at least 25. If the hitherto published chemical work on the atomic weight of radium is in any way near the truth, this cannot be the case. Similarly radium F must have an atomic weight less than radium, and it closely resembles bismuth in all its properties. If the atomic weight of radium is 226·5, it seems certain that bismuth and radium F must occupy the same space. There are only two other possibilities. A somewhat similar table, put forward by Meyer and Schweidler in 1906, assumes that uranium contains in reality a second element of much greater atomic weight, about 260, and that radium has the corresponding weight 255. In the second place, disintegration may result in the combination of two or more atoms of the product, giving an element of higher atomic weight; in this case, the active elements will not appear in consecutive series in the periodic table.

The second part of this paper will contain a full account of radium and its emanation.

The third part will include a description of the experimental production of transformation or transmutation of elements.

THE ACTION OF ALCOHOL[1]

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IT is but seldom in the study of medical science that one has to treat of a question of such widespread interest, and, as I believe, of such paramount national importance as we have before us to-day, and it is to be deplored that the medical profession has hitherto been able to answer only with uncertain voice, or, I might say, with two voices, the persistent demand for its opinion of the value of alcohol in therapeutics and in diet.

This fatal lack of unanimity is to be ascribed in the first place to the feeling that alcohol has not proved devoid of usefulness in therapeutics in the past, and that we must not be hurried into its dismissal from the sphere of medicinal agents without due consideration; and the denial of its value in disease has been in many cases too absolute, and has, in fact, provoked a reaction in its favour in some minds that were perhaps prepared to accept a more restricted use of alcohol as a remedy than has hitherto prevailed. The greatest possible advance in the crusade against the abuse of alcohol would be made, I think, if we could agree upon some formula that could be generally accepted, and I am not without hope that this meeting may make some progress towards this solution.

Another cause of confusion in the response of medicine to inquiry regarding the value of alcohol arises from ambiguity in the use of terms. We are too apt to apply the term "stimulant" to anything that promotes exhilaration and animation, and dissipates what the eighteenth century called the spleen, and to regard the result as evidence of health and vigour. But stimulant is also used, in a more exact sense, to indicate anything augmenting the activity of definite organs. It would, I think, conduce to more general agreement if the word could be used strictly in this narrower sense in discussing the question of alcohol, and if its effects, beneficial or otherwise, were always referred to each individual organ.

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[1] A paper read before the Section of Physiology at the British Association, Leicester, 1907.

Alcohol affects so many functions of the body that it is impossible to take them all up in the time at my disposal, and I shall therefore limit my observations to its action on nutrition, on the brain, and on the circulation.

Its effects on nutrition are ascribed in part to its influencing the digestion and absorption of ordinary foods, and in part to its acting as a food itself. As to the first, its effects on the digestive processes, there is a very general belief, supported by apostolic authority, that alcohol improves digestion. A large number of painstaking investigations have been carried out without fully confirming the popular view, however. It is true that the digestive ferments have been found to be accelerated by very small quantities of pure alcohol, but the acceleration is very small in degree, and is not observed when the forms of alcohol in ordinary use are substituted for the pure spirit, nor when this itself is added in quantities corresponding to one to two glasses of whiskey in man. As to the secretion of the digestive fluids under alcohol, it has been repeatedly found that alcohol after absorption induces a flow of gastric juice, but this is devoid of, or poor in ferments, and can scarcely promote the preparation of food for absorption. The movements of the stomach and intestine may perhaps be more active after alcohol has been swallowed in a concentrated form, and this may perhaps be the basis of the after-dinner liqueur. And some evidence is presented that alcohol accelerates absorption from the intestine, as is true of many other slightly irritant bodies.

The effects of alcohol on the digestion are therefore complex, for almost every factor in the process is altered in activity to a small extent when moderate quantities are taken. When one remembers, in addition, that the greatest influence of all on digestion is exercised by the taste and odour of the food, one is prepared for great divergences in the effects of alcohol in man. And this is the only inference that can be drawn from the results of clinical inquiry as to the value of alcohol as a stomachic in man. In some people the progress of digestion seems to be rather improved when wine is taken, but the improvement is small, while in others the reverse is true: the digestion is not accelerated, and may even be retarded by a couple of glasses of wine. The actual amount of food absorbed from the alimentary tract is scarcely changed definitely in either direction. But however variable the reaction of the individual stomach to small quantities of alcohol may be, there is only one response when larger quantities are taken, and that is disorganisation of the whole process. And while the usefulness of alcohol in treating some digestive disorders may still be uncontroverted, Binz's dictum, that the healthy stomach needs no stomachic, and therefore no alcohol, must be the standpoint of the physician to-day.

But it may be argued that while the absolutely normal stomach is capable of digesting thoroughly and extracting the whole of the nutriment from the food offered to it, the artificial conditions under which most of us live necessitate measures which are unnecessary in a more healthful environment. Does not the jaded appetite demand exceptional measures, and may not wine be used to render food palatable and promote gastric secretion and digestion just as other condiments are employed? Shall he who seasons his food with wine be condemned, while he who substitutes mustard may be regarded as of upright life and conversation? The objection to the habitual use of alcoholic beverages "for the stomach's sake," in the scriptural phrase, does not arise from its effects on the digestion, but from the tendency towards the habit being formed and from its action on the brain.

In regard to the second phase of the question of alcohol on nutrition—its food value—the last few years have witnessed experiments performed with such meticulous care that there can be but one opinion in the minds of those who have studied the subject. Over 95 per cent. of the alcohol ingested undergoes combustion in the tissues and is utilised by them as a source of energy. As regards its fate in the body, in fact, alcohol is strictly comparable to sugar, which is also an alcohol, though of a more complex nature than the substance under discussion. Like sugar, it is capable of supplying energy, which may be utilised in heat formation and mechanical work, and it may lead to the deposit of fat and to economy of the precious nitrogenous stores of the tissues. In fact, the more closely the metabolism under alcohol is examined, the more closely is it found to conform to that under an equivalent amount of carbohydrate, and it seems to me that the protagonists in the fight against alcohol can only harm their cause by still refusing to accept these results. For the recognition that alcohol resembles sugars and fats in its fate in the tissues by no means implies that it is a suitable food in disease or in health. The same is true of vinegar and even of morphine under certain conditions. Before an oxidisable substance can be contemplated as a substitute, therefore, it must be shown that, given in quantities which have any significance in calories, it has no greater possibilities for harm than normal foods. Can alcohol be taken without toxic effects on the tissues in general, quite apart from those on the brain and more specialised organs? On this point experiment has shown that when alcohol is substituted for other forms of food in persons unaccustomed to its use, it sometimes fails to act as an equivalent for some days, during which the deficiency has to be made up by the combustion of other available sources of energy. This has been supposed to indicate some specific toxic action of alcohol on the tissues; but there are grounds for believing that alcohol does not stand alone in this relation, but that the same phenomenon occurs when other unaccustomed but unimpeachable forms of food are suddenly substituted for those which the tissues have hitherto consumed. In this point, then, alcohol appears to behave in the same way as other nitrogen-free foods.

But another series of investigations has shown that alcohol leaves the tissues in an impaired state in regard to the measures which the organism normally takes to protect itself from injuries either by living organisms or by poisons. No experiments were needed to show that the abuse of alcohol lessens the resistance to invasion by pathogenic organisms; the records of pneumonia in our hospitals and of cholera in the East indicate this beyond the shadow of a doubt. But these fail to show beyond question that the habitual use of alcohol in small quantities, or its therapeutic use, has this effect; and the whole interest of the question at present lies in the dietetic use of alcohol as contrasted with the drunkard's abuse of it. A number of animal experiments on the subject have been performed by inoculations of pathogenic bacteria, or of their toxines, before or after the administration of alcohol, the mortality being compared with that of animals inoculated in the same way but not treated with alcohol. In these the results have almost uniformly been arrayed against the use of alcohol, but, unfortunately, the quantities of alcohol given scarcely correspond to the moderate use in man. Even Laitinen gave his rabbits about 1 c.c. per kg., which would correspond to about 4–5 oz. of whisky per day in a man. This quantity was insufficient to cause symptoms of intoxication in his animals, but the corresponding ratio could scarcely be considered within the limits of moderation in man.[1] Some recent work by Reid Hunt bears closely on this question, in that he finds that the continued administration of alcohol in small quantities renders mice and guinea-pigs much more susceptible to the effects of acetonitril, a poison which acts by the liberation of hydrocyanic acid in the tissues. Hunt considers his results due to alcohol deranging the metabolism in certain directions, notably tending towards an acceleration of some oxidative functions. And in this he sees a specific difference between alcohol and the carbohydrates, in that these have of course no such influence on the metabolic processes.

Hunt states that these changes arise from quantities of alcohol which correspond to that indulged in by "moderate drinkers," inasmuch as his animals showed no signs of intoxication. But a drop of alcohol per day for a mouse corresponds to an immoderate use in man; and in view of the importance of his evidence, it is extremely desirable that a more accurate determination of the amounts of alcohol given were available. For while I think there can be no question that alcohol in excess reduces the resistance of the general tissues to disease and may be deleterious to them in other ways, as Hunt's results indicate, it still remains undecided what is the lowest point in alcohol administration capable of inducing these effects.

On the whole, it must be conceded that small quantities of alcohol have not been proved to act deleteriously on the tissues in general, but, on the other hand, the threshold below which alcohol is innocuous has not been ascertained with accuracy, and probably lies nearer the limit of "moderate use" than is generally recognised.[2]

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[1] Since this paper was written, a further series of experiments has been published by Laitinen, who finds that the prolonged administration to animals of quantities of alcohol corresponding to less than a glassful of whiskey or two glasses of port wine per day in man, exercise a distinctly deleterious action on the blood, and reduce the resistance to infection.

[2] In view of the statement made by Professor Reid Hunt during the discussion of this paper and the later publication by Laitinen just mentioned, I

The effects of alcohol on the central nervous system differ very considerably in different individuals. In the lower animals they are marked by depression, the symptoms being exactly similar to those of chloral or of the other narcotics. Occasionally, a transient excitation occurs, but this is due to the irritant action in the stomach, and is absent when more dilute solutions are administered, or when the alcohol is ingested in small repeated doses. In human beings the same depressant effect is often seen, the first symptoms being more or less drowsiness and heaviness, which subsequently pass into slumber. But in the majority of cases the first effects elicited are feelings of good fellowship, well-being, and liveliness, with increased confidence in the mental and physical powers. The face is flushed, the eyes bright, and the pulse and respiration are accelerated. Larger quantities lead to uncertainty and inco-ordination of the movements, shown in difficult and stammering speech and staggering gait, and still larger amounts induce sleep and narcosis, which may pass into complete anæsthesia, and eventually prove fatal. The symptoms of intoxication, therefore, appear to differ in the lower animals and in man, for while in the former there are generally no signs of excitement, in the latter this feature may be very marked in the beginning. And even in man the effects of alcohol offer marked contrasts in different individuals, and in the same individual at different times. For the excitement is very much more marked when drinking is indulged in in company with others, while when alcohol is taken with less exhilarating environments or in solitude, the excitement stage is very much less marked or may be entirely absent.

The effects of alcohol on the brain have been explained in two different ways: the view which appears at first sight to be the more natural one, is that it first stimulates the cerebral cells to greater activity and then depresses them; that is, alcohol is believed to act on the cerebral grey matter in the same way as strychnine on the spinal cord. And this view, that alcohol is a central nervous stimulant, is still widely

feel that this paragraph requires modification. The very moderate use of alcohol (by which I mean the habitual daily consumption of one or two glasses of port, one or two pints of beer, or a glass of whiskey) appears from the researches of these authorities to induce definite deterioration of the tissues, and to render them more susceptible to attack by disease.

entertained both by the laity and by clinicians, while the majority of experimental observers rather lean to the view suggested by Schmiedeberg and supported by Bunge, Kraepelin, and many others, that the stimulation of the brain is only apparent. According to this theory, the excitement is caused, not by the augmented vitality of the nerve cells, but by a loss of the associations which ordinarily retard the expression of mental activity.[1] To adopt a mechanical simile, the brain may be compared to an engine fitted with powerful brakes. An acceleration of the motion may be due either to increased power of the engine (stimulation) or to the brakes being taken off, and it may be difficult for an onlooker to determine which is the true explanation. The apparent evidences of increased mental activity under alcohol, however, have proved for the most part illusory, when carefully investigated. The closer one approaches to the engine, the more evident it becomes that what appeared to be the result of increased power is really the effect of the removal of the brakes.

One argument against the stimulant action of alcohol is the narrow limits to which it is confined. All the recognised central nervous stimulants act on some particular part in small doses, but when larger amounts are ingested the stimulant action spreads over a wider area of the central nervous system, and gives rise to the symptoms characteristic of stimulation of that area. Caffeine, for example, first stimulates the mental functions apparently, but in larger quantities involves the motor sphere of the brain, and may finally stimulate the cells of the cord. Alcohol, on the other hand, appears to have only a depressant action on the nervous tissues, except in the human cerebrum. It is true that the exceptional development of the human brain might permit of a departure which is without analogy in other forms of poisoning.

But when the excitement stage is more closely investigated, it becomes apparent that all the cerebral functions are not facilitated by alcohol. It is common knowledge that under the influence of alcohol an individual may be more brilliant in conversation, more witty, more social, more generous in sentiment, but that he is not so careful in his statements, and has not that consideration for his own position or that of others which he ordinarily manifests.

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[1] When it was propounded the rôle of inhibition in the central nervous system was not appreciated, or at any rate had not been experimentally demonstrated. The recent work of Sherrington has, however, shown that every movement involves motor and inhibitory impulses, and seems to give a firm basis for the depression theory of alcohol.

The normal adult, in an environment which in a child would cause every symptom of exhilaration, maintains his self-control, partly because the position has lost its novelty, that is, he has associations which are wanting in the child, partly because the exuberance and gesticulations natural to the child are kept in check by his sense of the ridiculousness of these manifestations in later years. Remove the inhibiting associations, destroy the self-control of adult life, and the man becomes a child again in his sense of exhilaration and symptoms of excitement. The symptoms of intoxication which are ordinarily regarded as indicating stimulation of the brain do not necessarily involve this interpretation, but may be explained by a removal of those associations which ordinarily inhibit the external manifestations of emotion.

In a word, it is generally recognised that some of the highest functions of the brain are thrown out of action by alcohol administered in quantities which induce the phase of exhilaration. The further question is: What functions are actually increased in activity, and how far is this increase dependent upon the reduced activity of the processes which are depressed by alcohol?

Much valuable evidence as to the effect of alcohol on mental processes has been gathered in the psychological laboratories, especially by Kraepelin and his pupils, who have subjected the question to a large number of ingenious psychological tests. Thus it is found that typesetters do a smaller amount of work and make a much larger number of misprints when even a couple of glasses of beer are allowed, than when they perform their work without this drug. When a student was set to learn a number of meaningless syllables or a row of figures, he took a longer time to do so and made more errors in repeating them under alcohol than normally. Similarly, arithmetical calculations of all kinds were carried out much more slowly and with more errors, and the writing was slower and gave the impression of being that of an uneducated person who seldom had occasion to use his pen. Only in one respect was any increased aptitude shown—namely, in the transformation of an idea into movement. And many ergographic experiments appear to show that small quantities of alcohol have the effect of temporarily increasing the capacity of doing muscular work, especially when the subject is fatigued. This augmentation is only transient, and the total work done in the course of the day is considerably reduced by alcohol, as has long been demonstrated in the case of forced marching. These might suggest the view that the motor cells are first put in a state of greater activity by the direct action of alcohol on them, but another explanation is equally applicable, namely, that an ordinary movement is hampered by a series of associations, and that when these are destroyed by alcohol the movement may be carried out more quickly. At the same time, the associations in ordinary life not only retard the movement but also restrict and direct it, and the result of their absence under alcohol is shown by the awkwardness and inaccuracy with which the movement is executed.

It is noteworthy that in these experiments those mental processes which were ordinarily performed readily were less retarded than others in which the subject was less practised and which required more effort. That is, the powers most recently acquired and most readily lost are those on which alcohol first acts, while those operations which have become habitual are less impaired. This is in complete accord with what is observed in the earlier stage of intoxication or exhilaration. The most recent acquisitions in adult life are the power of self-control and the feeling of self-respect, which are manifested in regard for the conventions of life, and in the prudence which leads one to avoid many procedures which in earlier life might have been indulged in without reproach. And under alcohol these are the first mental processes to be disordered. *In vino veritas*, in intoxication the natural man is exposed, stripped of the trammels of convention, and robbed of the fruits of experience and education.

Many other results of these experiments are of interest, but cannot be entered on here. One feature which bears a familiar aspect, and which was brought out clearly in many instances, is the confidence of the subject of the experiment that his efforts were unusually successful under alcohol, while the impartial record showed results far below the level attained during abstinence.

In all of these experiments the amount of alcohol taken was small, in no case sufficient to induce any of the more evident symptoms of intoxication. It is therefore of great interest to find in the later publications of Kraepelin's laboratory, that distinct impairment of the psychical powers was found to persist for a much longer time than would be anticipated; the average efficiency was not regained until from twelve to twenty-four hours had elapsed after the alcohol had been taken. If this proves to be true in the case of persons who have acquired a tolerance for alcohol, even moderate drinkers are never completely normal, their mental powers never recovering entirely from one dose of alcohol before the next is taken.

The results of these investigations on the mental state under alcohol, as well as many others which I have not discussed, appear to place the theory that alcohol acts as a narcotic upon a firm basis. I do not hold that it is absolutely determined, but some more satisfactory evidence must be brought forward in favour of the stimulation theory before it can be considered as a rival to that of Schmiedeberg. And this evidence must define what functions are stimulated, and must not be a repetition of the old statement, that the tone and vigour of the nervous system are maintained by alcohol.

But if the chief or even the whole action of alcohol on the brain were proved to be a narcotic one, this would not preclude its use in therapeutics. For here the chief object in the use of alcohol is not to induce but to repress cerebral activity, and the alleged stimulant action arises from a confusion of ideas; a similar confusion is met with in regard to opium, which was also regarded as possessing stimulant properties which recommended its use in acute diseases accompanied by cerebral symptoms. The result of both drugs is in reality cerebral depression, which manifests itself in a condition of euphoria. The disease often loses its strongest ally when the anxiety and worry of the patient are allayed by alcohol. He feels less concern and more resignation, not because his soul rises triumphant through the stimulant action of alcohol, but through his brain being less capable of dwelling on his disabilities, because it is partially narcotised.

Alcohol, therefore, is not to be regarded as exercising any unique action on the brain in disease, but resembles the other narcotics, and as a remedy must be compared with these. And on the whole it emerges from the ordeal as not inferior in many points. Thus, none of them disturb the digestive tract less, and most of them exercise a more depressant effect on the centres in the medulla oblongata; for I think it may be taken as proved that in ordinary therapeutic doses alcohol does not depress the respiration, but, on the whole, tends to augment it even when no excitement is induced. Where a slight narcosis, sufficient to allay anxiety and induce rest is required, then, alcohol deserves consideration, but it is less certain in effecting a more marked depression, for which it cannot be compared with the modern narcotics.

The effects of alcohol on the circulation have long been a matter of dispute, many clinicians holding that in failure of the heart and vasomotor centre alcohol is of service, while others have found that it may be dispensed with. The experimental results have recently been discussed by Dixon, who suggests that alcohol may support the heart by acting as a food-stuff, and may thus increase the blood-pressure and improve the circulation. It is true that another observer has not been able to satisfy himself that alcohol acts as a food for the heart, but Dixon's results unquestionably re-open the question of the usefulness of alcohol in the treatment of acute circulatory failure, in regard to which a sceptical attitude has more recently been adopted by many of the leaders of the medical profession. And in addition to any direct action on the circulation, alcohol may prove of value in circulatory failure through its narcotic action in the same way as opium, over which it has the advantage of not inducing any embarrassment of the respiration.

To sum up, alcohol may be of some value in therapeutics as an adjuvant to foods, in order to render them more attractive, and thus improve their digestion, and also possesses some food value itself. It acts as a cerebral depressant, and may be useful in certain diseases in this way, and it may perhaps aid the failing heart. A small dose exercises no definite demonstrable poisonous effects on the tissues, and small repeated doses, though suspect, have not been shown to be deleterious.[1] If alcohol were a new synthetic remedy fresh from Germany, it might probably be hailed as a useful addition to therapeutics, but its popularity as a remedy would be short-lived. Not because of its failure to substantiate its claims as a narcotic, nor because it had proved fatal in the hands of physicians, but because an alcohol habit had been developed in some of the population. If one considers the few sporadic cases in which sulphonal or cocaine, for example, has given rise to a habit, and the discredit into which it has fallen in consequence, and compares the cases of disaster from alcohol met with every day, one cannot but feel that the drugs have been weighed in very unequal scales, and that any one who discards cocaine—undoubtedly a drug of great value—must, to be consistent, condemn the use of alcohol. This seems to me to be the ground on which we must take our stand. Alcohol is a drug which may be useful in therapeutics, although I think it can hardly be considered indispensable, but which has so often given rise to habit that its use must be curtailed to the utmost limit. In some conditions, as in old age and debility, it may be justifiable to neglect its drawbacks, exactly as in some forms of malignant disease the patient may be allowed to contract the morphine habit; but let us at any rate advise it here with eyes open to the risks run, and with the recognition that we are prescribing a drug and not merely a placebo. It may be argued that alcoholism has almost never arisen from the therapeutic use of the drug, and it is true that the responsibility for alcoholism does not rest upon the medical profession in the same way as that for morphinism or cocainism. But the public are justified in regarding alcohol not as a drug, but as an article of diet, as long as the physicians order it in the casual way which is familiar to all of us. How often is alcohol not ordered but allowed by the medical man at the suggestion of the patient, and how many physicians allow it, not believing that it will do any good, but assuming that it will do no harm, and even not hesitating to make the statement! The laity can hardly be blamed for ignoring the evidences of danger presented daily in their streets, if their scientific mentors themselves adopt this ambiguous position, and the medical profession cannot complain if they are accused of indifference towards the greatest evil of their country and their age.

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[1] But see footnote, p. 554.

THE THEORY OF DIABOLO

BY C. V. BOYS, F.R.S.

IT would be an interesting subject for a course of lectures or a series of articles to trace the effects of rotation in balls and other objects used in games and in other pursuits. Some of these are fairly obvious, as, for instance, the effect of a spin on a cricket-ball causing it to break after contact with the ground, or the effect of a screw in billiards, where the ball has a rotation about an inclined axis and bounces from the cushion at an angle which by no means obeys the laws of reflection. Here also, in consequence of the rotation the height of the cushion has to be seven-tenths of the diameter of the ball, for in the case of pure rolling the upper part of the ball may be considered to be travelling more quickly than the lower part, and so, if the cushion were only the height of the centre the upper part of the ball would go on and take the rest of the ball with it. Less simple than these are the effects of the air in causing a spinning ball to veer away from the course that it would take if it did not spin. The best known of these is that shown by the flight of a golf-ball, which was first carefully investigated by the late Professor Tait. When the ball is fairly struck by the club, the front face of which slopes somewhat backwards, it is struck at a point below its centre. The rotation imparted is in such a direction as to cause the lower part to move forward most quickly and the front part to move upward. At one time it was supposed, and I believe clearly proved in the armchair in an analogous case, that the front portion moving upward would cause the ball to roll, as it were, upon the air compressed in front of it, and so cause a departure from the natural trajectory, which in the case of the golf-ball would be downwards. As every one knows, the exact reverse is the case, and a proper consideration of the action shows that it should be so, for the air-pressure can be shown, both by theory and by experiment, to be greater below a ball spinning and moving in the directions followed by a golf-ball than above. Professor Tait established the fact that upward forces due to this cause may be set up which are two or three times as great as the weight of the ball. Another example of this, but less easily followed, is the flight of a spherical bullet from a bent smooth-bore barrel. If such a barrel is curved in a horizontal plane so as to be suitable, according to the story of our childhood, for shooting any one round a haystack, the bullet, far from continuing the curve which it was compelled to follow in the barrel, acquires therein a spin, owing to its rolling along on the concave side, and this spin produces a curvature when free opposite in kind to that of the barrel that gave the rotation. Such a curved flight of a ball is well known in games; the light ball of lawn-tennis when well cut follows a markedly curved course, and, best of all, the child's india-rubber air-ball or balloon when cut by a sweeping stroke of the hand curves rapidly upwards in its flight and provides the material for an excellent and violent indoor winter game.

Mysterious as some of these air-effects may be, they are wholly eclipsed by the queer and apparently semi-contradictory effects of the rotation of a body which are noticed when anything is done to twist the axis of rotation into some other direction. If a grown-up and otherwise well-educated man had never seen a top spin, and, being familiar with the fact that such a body will not stand up upon its point when not spinning, and with the whole science of statics, were suddenly presented with the phenomenon of a spinning-top it is difficult to realise, familiar as we are with the result from our earliest childhood, how great would be his surprise. The fact that it should stand up at all would seem sufficiently uncanny, but its gentle gyrations round the upright position, more rapid as the rate of spin diminishes, would seem to defy explanation. It is only universal familiarity with the phenomenon that prevents surprise or any anxiety in the majority of people to dissolve the mystery. It would be out of place in an article such as this to prove from the simple laws of motion propounded by Newton that a top should spin as it does, or, more generally, how any spinning body will behave when any forces are applied to it which would, if it were not spinning, move the axis about which it happens to be turning into some different direction. This subject is treated in a charming manner by Professor Perry in his book on *Spinning-Tops* and by Professor Worthington in his *Dynamics of Rotation*, and with rigid accuracy by Professor Greenhill in his articles in the *Encyclopædia Britannica*. It is sufficient here to state shortly the facts. Take the case of the spinning-top. This, if not spinning, would fall over, the toppling-over effect of gravity being greater as the inclination is greater. When the top is spinning the forces due to gravity are the same as before, tending to drag the axis of spin over and downwards, but in consequence of the spin it has a different effect: the axis does not move downwards but sideways, always at right angles to the direction in which it is urged, and so the top gyrates. Further, the rate of moving sideways is greater as the rate of spin is less. If the point on which the top spins is adjustable so that it may be made to project more or less, or may be withdrawn until it is above the centre of gravity, then as it is fixed nearer to the centre of gravity the toppling effect of gravity will be less and the top will gyrate more slowly. When the point on which it spins is at the centre of gravity the toppling effect of gravity is destroyed, and so it ceases to gyrate, and when the point is raised higher still gravity tends to topple no more, but to set it upright: it then gyrates the other way. When gravity acts so as to make it fall it gyrates in the same direction as it spins; when gravity acts so as to set it upright it gyrates in the opposite direction. An example of a slow gyration of this sort is presented by the earth, which would, if it were spherical, maintain the direction of its axis of rotation indefinitely. Any star in the line of this axis would be for all time the pole star. Both the sun and moon in their attraction upon the "equatorial protuberance," or excess of matter outside the sphere, act in such a manner as to drag it towards the plane of the ecliptic, or the earth's orbit round the sun. If this is looked upon as a level, then the sun and moon act together so as to set the top upright. The gyrations then are in the opposite direction to the spin, which is also the direction of revolution round the sun, and so the "equinoxes precess." The pole of the earth describes a circle round the pole of the ecliptic once in about twenty-six thousand years.

When a spinning body of other shape than a ball is projected through the air, the effects of the air upon the direction of the axis of spin, and hence on the motion of the body, give rise to numerous interesting problems. For instance, a disc spun and thrown by the right hand edgeways turns so that the right side of it rises and it veers to the left; on the other hand, a boomerang started with the same motion rises and comes back again. An elongated bullet neither follows the trajectory, like an arrow, nor maintains the direction of its axis, but conically screws itself round a line slightly above the trajectory. Whenever a spinning body is projected through the air which is in any respect different in its conditions from other cases which have been investigated, a new problem is almost certain to be found, and it is not safe to jump to conclusions.

In the case of the diabolo spool there are really no difficulties, because the air-effects are barely noticeable, and they are of the simple kind observed with golf-balls, tending to deflect the spool to the right as it falls if it is spinning rapidly with a right-hand spin. Ordinarily, in the draughty and eddying enclosures called gardens attached to houses in London, this deviation from a straight fall is not easy to detect, and it certainly is of no importance in the game. If, however, the spool were much lighter, and were ribbed or roughened like a golf-ball, the air-effect would be increased.

With an ordinary spool, the form of which it is unnecessary to define, the centre of gravity is above the string support. It is therefore unstable, and on whichever side it happens to incline, on that side, if not spinning, it will fall. Gravity acts in such a manner as to topple the axis of spin over towards a vertical direction. With the usual right-hand spin the hands are moved in such manner that the string is jerked tight when the right hand is rising, and is loose when it is falling, and the spool gets its support mainly while the string under it is moving from left to right. The upper part, therefore, moves from right to left. In order to correct the level of the axis, when for any reason this ceases to be level, it is necessary to apply forces twisting it not in the desired direction, but in a direction at right angles thereto. Any child will tell you to put the left hand forward if the far end is drooping. Putting the left hand forward means the application of a twist on the axis, tending to turn the far end to the right. This may be proved in a moment by placing the spool on the ground with the string under it and then gradually lifting it with the left hand forward. It will then, not being in a condition of spin, immediately turn so that the far end moves to the right. If the left hand is put forward when the spool is spinning, the effect of the tendency to twist to the right is a movement in a direction at right angles to the tendency, and the far end rises. There are two directions at right angles to this tendency, one upward and one downward. It is puzzling sometimes to know which right angle will be followed. In the present case it is easy to tell by reference to the known movement of a top. Consider the axis of the spool to be the axis of the top and the far end to be the support of the top, or point on which it is spinning in an anti-clockwise direction, the direction of gravity being supposed for the moment away from you. The action of the string tending to turn the far end to the right or the near end to the left corresponds to the action of gravity on the top when it is leaning to the left, tending to make it fall more to the left. It does not do so, but moves sideways in the direction of the spin, *i.e.* actually towards the earth; or, in other words, the other end, or far end, is raised. If the spin is left-handed of course the result is reversed, and so it is a pity when learning and acquiring the habit to base it upon a consideration which must be reversed when the direction of spin is reversed. The better instruction to follow is to jerk the business hand toward the high side—it being understood, of course, that the business hand is the one which, by its upward jerk, imparts the spin. With such a rule as the early guide the instinct, which is quicker than the recollection and application of any rule, is from the first directed aright, and no conscious effort of reversal is needed whether the direction of spin is right or left handed or the near or the far end is falling.

In order not to be tied to the crab-like method of playing sideways, which is so often seen, it is well to practise playing with a right or left spin indifferently. If playing alone, the change may be brought about by moving round to the side of the spool which is moving upwards and catching the spool on the stick held by the passive hand, then in running the spool down on to the string it will be found to be reversed in direction as seen by the player, but not as regards the points of the compass. This catching on the passive stick is more easily effected, at first, at any rate, by catching on the active stick first and then catching it on the passive stick. The direction of spin may also be reversed by throwing the spool up and turning half round before catching it on the string. Quite a moderate amount of practice, reversing every time by one or other method, makes the direction of spin a matter of perfect indifference.

I have already referred to the fact that it is necessary for the player to make a half-turn if he would face the spool between every reversal. This is merely another way of saying that the spool maintains its direction in space—that is, it does so if it is perfectly balanced. It is impossible in that case, and provided that it is kept level, to get the spool to veer round to any appreciable extent. If the disturbances were a good deal less than they are, it would in this country appear to follow the sun, but at the reduced rate of nearly 12° per hour, in consequence of the rotation of the earth. Though such accuracy is beyond practical attainment, the persistence of direction is very marked. If while spinning the diabolo a person walks round the garden, he will soon find he is getting his arms involved with one another, as the spool will not turn and the sticks must not either. Or if while travelling in the railway along a curve a passenger is spinning a diabolo and maintaining it level, the apparent turning of the spool will indicate the actual turning of the carriage in the opposite direction. A good place to try this is in the "Bakerloo" tube where it enters the Regent's Park in its northward journey, or in the Hampstead tube in the Euston district.

I have insisted upon the necessity of keeping the spool level when making this experiment. Suppose, for instance, that the far end is down a little and that the usual right-hand spin is being applied, then, as the far end is down to a certain extent, the centre of gravity, instead of being above the string, is on the far side of this position, and gravity tends to topple the spool over on the far side—*i.e.* to turn the spinning axis so that the far end moves downwards. Just as the tendency of the string support to turn the far end to the right makes it actually rise, as already explained, so this tendency of gravity to make the far end move downwards causes it, in consequence of its rotation, to go sideways, and the particular sideways in this case is to the right. If, then, a player desires to work the spool round he has merely, by thrusting one hand forward, to make one end dip somewhat, and then to keep spinning it in that position, when it will veer round—more quickly if the spin is slow—and then, when it has the required direction, to bring the low end up again by drawing the same hand towards himself. It does not matter whether the spin is right or left handed; if the right hand is put forward to cause one end to dip, the spool will then veer to the right, and *vice versa*, for the end that dips is reversed with a reversed direction of spin, and the action of the reversed tendency to fall, combined with the reversal of spin, gives the same direction of veering. This process was described by a speaker at the Physical Society at a recent meeting where I was showing a peculiar spool, to which I shall next refer.

An ordinary fly-wheel or a disc is twice as effective as a fly-wheel if it is mounted to spin in its own plane, as it would be if it were made to spin on one diameter as an axis. Its moment of inertia is said to be twice as great when spinning as it does in practice as it would be if made to spin about a transverse axis. On the other hand, a diabolo spool or an elongated bullet is less effective as a fly-wheel when spinning about its axis of rotational symmetry. In these cases the moment of inertia is a minimum, while in the former it was a maximum when spinning in the usual manner. Anything, whatever shape it may have, must have some direction about which the moment of inertia is a maximum or a minimum, and it may have a single transverse axis about which it is correspondingly a minimum or a maximum.

If any body is set spinning about any axis and then liberated, it will continue to spin about that axis and resist disturbance only if the axis of spin is one of maximum or minimum moment of inertia. If the body were spun about any inclined axis and liberated, then, according to the position in the body of the inclined axis and the relative values of the maximum and minimum moments of inertia, the axis about which it thereafter is momentarily spinning will move within the body according to one curve and in space according to another, for which an explanation must be sought in Maxwell's Collected Works, vol. i. p. 248. If, on the other hand, the spinning body were a uniform sphere, in which the moments of inertia about all diametrical axes are alike, it would have no tendency to move the axis of spin in any particular manner within itself, and any disturbance would set this axis wandering in the sphere, or, as Maxwell put it, the sphere has no dynamical backbone.

It is not necessary in order that a thing should have equal moments of inertia in all directions that it should be spherical in shape. A long round thing has a minimum moment of inertia about its axis of symmetry, while a flat round thing has a maximum moment of inertia about this axis. A bullet or an ordinary diabolo spool is an instance of the former, while a fly-wheel or a disc is an instance of the latter. A diabolo spool need not have the usual angle of about 70°, it may be made longer or wider. As it is made wider the moments of inertia in the two directions become gradually more alike, and if it were made wide enough it would correspond in this sense to a fly-wheel, and the respective values would be inverted. There must be, therefore, some intermediate width or angle of cone which makes the moments of inertia in all directions the same, so that dynamically it is the same as a sphere.

It is easy to prove that in the case of a thin hollow double cone, with the ends open and joined point to point, the proportion which gives the spherical characteristic is reached when the angle of the cone is nearly 110°, or when the tangent of the semi-vertical angle is $\sqrt{2}$. All matter added to such an ideal skeleton, without it equatorially makes the axis of rotational symmetry an axis of maximum moment of inertia, all added beyond in the direction of the axis makes this a minimum. A judicious addition of matter without and beyond leaves the double cone dynamically the same as a sphere. If, then, a spool is made of this angle, and of such a thickness as to give a convenient neck for the string by addition of matter without the ideal cone, and by the addition of about the same amount beyond the ideal cone, the resulting spool will be dynamically very nearly a sphere. It is best to make it with an axial hole and with a very slight preponderance of matter without the ideal cone. The moment of inertia about the axis of spin is then just a maximum, and the spool spins perfectly. A number of sticks may then be made of different lengths and thrust centrally, one at a time, into the hole. If any one of these is so exactly chosen in length as to make the moments of inertia in all directions the same, then spinning becomes impossible for the reasons given. In order to ascertain if any stick is too long or too short it is merely necessary to suspend the combination from a torsion wire so as to oscillate about the axis of rotational symmetry and about a transverse axis successively. Then if the time of oscillation about the former is the greater, the stick is too short, and *vice versa*. In order to make spinning really hopeless the time of oscillation should not differ by anything like so much as 1 per cent., but when equality to this extent is reached the spool becomes sufficiently unmanageable.

When a stick has been properly adjusted the equality fails if the stick is not centrally placed, and the spool can be spun again quite easily. Now, however, being out of balance, the heavy end in tending to fall actually goes sideways, and more quickly so at starting, when the spinning is slow. With a right-hand spin the heavy end, whichever way it is pointing, veers to the right. This may, of course, be equally well shown with any spool which is unbalanced, or which is made so by attaching a nail or a lump of wax to one end. A stick too short to give the spherical property when centrally placed may, nevertheless, do this when pushed out of centre, and then, though the combination will spin perfectly in the first position it is impossible in the second.

It might be thought that the ball in the game cup-and-ball, which at least is a sphere in fact, should not maintain its axis when spun with a view of being caught on the point. But here there are two answers. The first is that though outwardly a sphere the axial hole made for the point to enter destroys its spherical properties. This may be the case to the extent of an inequality in the moments of inertia of perhaps as much as 5 per cent., and this is quite enough to give stability. I have, however, turned a groove in the equator of a well-made ball of this kind to such an extent as to bring the moments of inertia the same, at least to a small fraction of 1 per cent. I was rather surprised to find that I caught this sophisticated ball the first time I tried it. The case, however, is not parallel with the diabolo spool in this respect. While the tweaking of the string on the spool is certain not to be exactly symmetrical and free from disturbing influences, the axial string from which the ball is suspended lifts it when spinning with a pull which must be as truly axial as the turned work is round, and so the disturbance, if any, must be so slight that the ball, in the short time that it is free, has no time to take up an appreciably different position before it is caught. All the time that it is on the string it is held true, while, on the other hand, the spool is only supported and tweaked by the string a very small fraction of the whole time.

Of all the appliances in the class-room for illustrating the precessional properties of rotating bodies I do not know one which is so inexpensive, simple, and handy as the now popular diabolo. It is whispered that mathematical professors do not always illustrate what they wish very successfully when using gyrostats and Maxwell and other tops. The diabolo seems to have been invented for their special benefit. A complete and proper demonstration of the points described above, and of many others, no doubt, would add enormously to the joy of the class. If at any time the spool should prove refractory the expositor could fall back upon the convenient formula tan $\theta = \sqrt{2}$, which in time might be contracted to tan, and would so serve the double purpose of an explanation and a harmless but comforting expletive. As a game I do not at all feel inclined to agree with the view that it is not worth while, that it is silly, that it is a mere passing craze. It may, and no doubt will, go out of fashion as quickly as it came in, if indeed it has not already done so, but that is not the fault of the game but of society, who equally threw over cycling before the motor car had destroyed that invigorating pursuit.

SYNTHETICAL DRUGS

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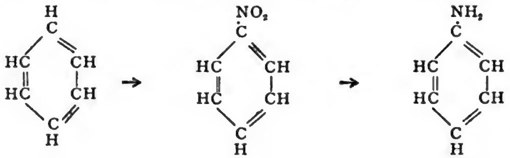
THE medicaments falling into the category of synthetical drugs are those which are built up by chemical means from simpler carbon compounds, and not extracted ready-formed from products of the vital activities of plants or animals. In this article it is intended to discuss in simple terms the chemical nature of a typical selection of these therapeutic agents, the trivial or commercial names of which are often household terms.

In 1906 chemists from all parts of the world gathered together in England to celebrate the jubilee of the coal-tar industry, the fiftieth anniversary of the discovery of the colouring matter, mauveine, by the late Sir William Perkin, and 1906 may also be regarded as the jubilee year of the synthetical drugs, for it was in an attempt to synthesise from aniline the valuable alkaloid, quinine, that Perkin discovered mauveine, his researches on aniline being the pioneers of other investigations which led to the employment of this remarkable base, aniline, in the production of compounds of therapeutic value. It is therefore, at the outset, necessary to consider, even though very briefly, the chemistry of aniline and its parent hydrocarbon, benzene. The latter substance, discovered by Faraday in 1825, is the chief constituent of the volatile oil obtained on distilling ordinary coal tar. Chemical analysis shows that the compound consists of twelve parts of carbon united with one part of hydrogen or, in the language of the atomic theory, one atom of carbon combined with one atom of hydrogen. Furthermore, a consideration of its vapour density and other physical properties indicates that a molecule of this hydrocarbon—that is, its smallest conceivable part—is somewhat complex and contains no less than six of these pairs of atoms. A general survey of the compounds of carbon shows that this element possesses in a marked degree the property of accumulating in the molecules of these substances. In certain organic compounds the carbon atoms are arranged in chains which are either straight or branching. If we consider one of these chains having six carbon atoms, and if we suppose further that the chain is coiled so that the ends meet like a snake with its tail in its mouth, we then get a representation of the carbon backbone of the benzene molecule. To each of these carbon vertebræ one of the hydrogen atoms is attached; and now to give the finishing touch to our benzene ring we must consider what is the usual habit of combination of carbon in the many substances in which it is present. Of the thousands of carbon compounds known there are scarcely any which furnish exceptions to the general rule that this element is quadrivalent, or in other words that its atom has four bonds or valencies with which to attach itself to other atoms.

The following graphical formula I. for benzene indicates one of several ways in which this condition is satisfied, this particular mode of representation being due to Kekulé:

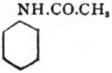


I. II. III.

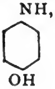
The double linkings represent points of great reactivity in the molecule, and their presence exerts a very profound influence on the chemical properties of benzene and its derivatives. It is, moreover, largely owing to these double linkings that benzene derivatives are so frequently of therapeutic importance. The physiological action of benzene itself is, however, only slight, the compound having merely the depressing hypnotic effect characteristic of the hydrocarbons in general.

ANTIPYRETICS

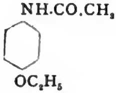
Aniline (formula III.) is derived from benzene by first treating the hydrocarbon with nitric acid whereby nitrobenzene (formula II.) is produced and then replacing the oxygen atoms in the latter compound by two hydrogen atoms. This process is called reduction, and is carried out very simply on a large scale by heating the nitrobenzene with iron filings suspended in slightly acidified water. Aniline resembles ammonia in some of its properties, for it is a base capable of yielding well crystallised salts such as aniline hydrochloride and sulphate. Both the base and its salts have a marked physiological action, and in fact they are powerful poisons. These substances have a beneficial effect in lowering the temperature and subduing pain, but on the other hand they have a very deleterious action on the red corpuscles of the blood, bringing about a destruction of the hæmoglobin. Aniline poisoning is characterised by the blue appearance of lips and nails, failure of respiration, giddiness, coma, and finally death. These acute symptoms are, however, considerably diminished by converting aniline into its acetyl derivative, acetanilide, a substance which has been employed as an antipyretic under the name of *antifebrin*[1] (formula IV.). This compound is readily prepared by heating together aniline and glacial acetic acid: $C_6H_5NH_2$, $CH_3 . CO_2H - H_2O = C_6H_5 . NH . CO . CH_3$.



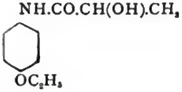
IV.



V.



VI.



VII.

It should, however, be borne in mind that the acetyl group $CO . CH_3$ is readily removed within the tissues either by hydrolysis or oxidation, so that aniline is regenerated, and its poisonous effect is produced only in a less acute form than when the base itself is administered. The continued exhibition of antifebrin is to be deprecated as likely in the long run to produce aniline poisoning. It has been found that aniline is converted in the system into para-aminophenol (formula V.), which is then eliminated in combination either with sulphuric acid or glycuronic acid $COH . [CH . OH]_4 . CO_2H$. This action of the organism in converting aniline into the less poisonous para-aminophenol has been taken into account in the production of the antipyretics of the phenacetin series.

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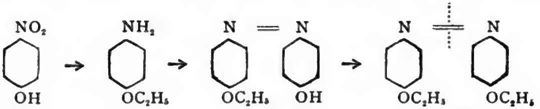
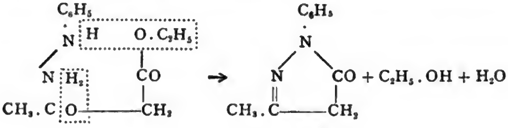
[1] The full graphical representation of the benzene ring or nucleus in formulæ I. to III. has now been simplified to the hexagon represented in formulæ IV., V., etc. It will be seen that this benzene nucleus is present in the majority of the synthetical drugs discussed in this article.

Phenacetin itself (formula VI.) is a febrifuge and an analgesic which is conveniently prepared by the following series of operations: Para-nitrophenol (VIII.) obtained as one of the products of the action of nitric acid on phenol (carbolic acid) is converted by treatment with ethyl sulphate (ethylation) into nitrophenetole $NO_2 . C_6H_4 . O . C_2H_5$, and this substance is reduced to phenetidine (IX.). This base when treated in succession with nitrous acid and an alkaline solution of phenol yields the complex compound (X), which is then ethylated to form the substance XI. It will now be noticed that the product XI. is symmetrical about the dotted line, and when it is reduced with tin and hydrochloric acid it splits into two parts at this point, each half taking up two hydrogen atoms and giving rise to a molecule of phenetidine (IX.). One molecule of phenetidine is made to undergo the series of changes represented by X. and XI., while the other molecule is acetylated and thus converted into phenacetin (VII.). This mode of procedure is adopted because of the difficulty of preparing pure paranitrophenol, and in this way an initially small amount of paranitrophenol can be made to produce a large quantity of phenacetin. This drug is somewhat sparingly soluble in cold water, but when the acetyl group is replaced by the lactyl group $CO . CH(OH) . CH_3$ derived from lactic acid a more soluble compound is produced to which the name *lactophenin* (formula VII.) is given. This substance has an antineuralgic action; its lactyl group is more readily split off than the acetyl group of phenacetin, and this change occurs under the influence of the acid gastric juices, whereas phenacetin, *methacetin* $NH(CO. CH_3). C_6H_4. OCH_3$, *triphenin*, and other substances of this series are hydrolysed only by the alkaline juices of the intestine.



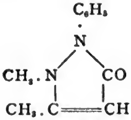
VIII. IX. X. XI.

Antipyrine, one of the most important drugs of this group, was originally discovered by Knorr in 1883 in an investigation on the condensation of phenylhydrazine, $C_6H_5 . NH . NH_2$, and ethyl acetoacetate, $CH_3CO . CH_2 . CO_2C_2H_5$. These two substances, the former of which is an aniline derivative whilst the latter may be regarded as a complex substance of the acetic acid series, interact to give rise to a compound containing a new ring in the manner indicated in the following diagram:

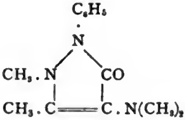


XII.

This product, phenylmethylpyrazolone (XII.), is physiologically inert, but on methylation (treatment with methyl iodide) it gives rise to phenyldimethylpyrazolone (XIII.) or antipyrine.



XIII.



XIV.

This compound is a valuable antipyretic and antineuralgic; it reduces febrile temperatures to the normal, and the subsequent rise of temperature is gradual and unaccompanied by shivering fits. The reduction of temperature is maintained for eight to twenty hours.

Knorr's good fortune in synthesising a therapeutic agent of this order is gauged by the fact that although many other derivatives of the pyrazolone series have been prepared and patented as antipyretics, only one has shown itself to be of anything like the same value as antipyrine. The drug in question is the substance *pyramidon*, which has been placed on the market by the firm of Meister, Lucius & Brüning, who were also the first to prepare Knorr's antipyrine on a manufacturing scale. Pyramidon, dimethylamino-antipyrine (formula XIV.) is prepared by treating antipyrine with nitrous acid, reducing the resulting nitroso-antipyrine to amino-antipyrine and then finally methylating this base to obtain the required compound. This drug is thrice as active as antipyrine; its action begins more gradually and continues for a much longer time. It is prescribed in rheumatism, influenza, and typhoid fever; it forms salts with the acids of which the most important therapeutically are the salicylate and bicamphorate.

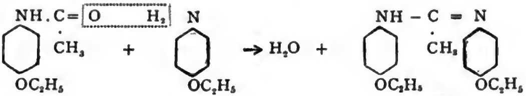
Migrainine, another drug of this series, is antipyrine-caffeine citrate; it is indicated in influenza, neuralgia, and insomnia.

Trigemine (M., L. & B.) is an additive product of pyramidon and butylchloral hydrate $CCl_3 . CH_2 . CH_2 . CH(OH)_2$ which has a marked analgesic action.

ANÆSTHETICS

Closely allied chemically to the phenacetin series are some of the cocaine substitutes employed to produce local anæsthesia.

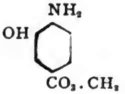
Holocaine is the hydrochloride of the base XV. produced by condensing phenacetin and phenetidine, $C_2H_5O . C_6H_4 . NH_2$. in the presence of phosphorus oxychloride, an agent which serves to remove a molecule of water in the manner indicated below



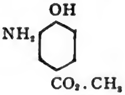
XV.

As an anæsthetic for operations on the eye its effect is prompt and lasting, and is not accompanied by mydriasis or disturbance of the accommodation of vision. On account of its toxic properties holocaine is not adapted for hypodermic use.

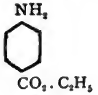
Orthoform (XVI.) and *new orthoform* (XVII.) are the names applied to two isomeric bases the latter of which is generally employed at present owing to its lower price. Like cocaine, these compounds render insensitive the nerve-endings and nerve-trunks with which they come into direct contact. This local anæsthesia is, however, not produced through the unbroken skin. A similar substance, *Anæsthesine*, ethyl para-aminobenzoate (XVIII.) is also employed as a local anæsthetic, and is non-irritant and non-toxic. The three foregoing compounds have been placed on the market by Messrs. Meister, Lucius & Brüning.



XVI.



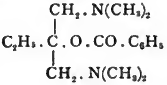
XVII.



XVIII.

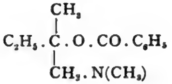
Novocaine, a derivative of anæsthesine having the formula $NH_2 . C_6H_4 . CO_2 . C_2H_4 . N(C_2H_5)_2$, HCl, is a powerful local non-irritant anæsthetic, seven times less toxic than cocaine, but somewhat transient in its effects.

Alypine, a local anæsthetic recently put forward by the Bayer Company, is the hydrochloride of tetramethyldiaminodimethylethylcarbinyl benzoate (XIX.).



$$\begin{array}{c} CH_2 . N(CH_3)_2 \\ | \\ C_2H_5 . C . O . CO . C_6H_5 \\ | \\ CH_2 . N(CH_3)_2 \end{array}$$

XIX.



$$\begin{array}{c} CH_3 \\ | \\ C_2H_5 . C . O . CO . C_6H_5 \\ | \\ CH_3 . N(CH_3) \end{array}$$

XX.

This drug has the useful properties of cocaine without its disadvantages, as even in large doses it does not injuriously affect the heart or respiration, and moreover it does not produce mydriasis.

Stovaine is the hydrochloride of a similar base (XX.); it is produced in the so-called Grignard reaction by the interaction of magnesium ethyl bromide and dimethylamino-acetone followed by benzoylation of the product.

HYPNOTICS

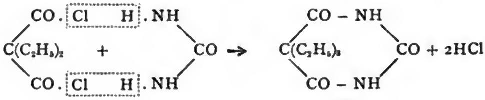
It has already been pointed out that the hydrocarbons themselves have slight hypnotic properties, which, however, become more pronounced when hydroxyl (OH) is introduced into the molecule. This increase in physiological activity is not, however, due to any narcotic action of hydroxyl, which on the contrary has a stimulating tendency. The opposing tendencies of the hydrocarbon and hydroxyl groups are illustrated by the well-known physiological action of ethyl alcohol. Morphine, again, owes its therapeutic action to the presence in its molecule of two hydroxyls, for when these are replaced by methoxyl or ethoxyl the narcotic properties of the alkaloid disappear.

In this connection the hydroxyl must be regarded as an unsaturated group owing to the presence of bivalent oxygen, and the physiological function of these unsaturated groups (hydroxyl, carbonyl, CO, and the doubly and trebly linked carbon atoms $>C=C<$ and $-C \equiv C-$) is to furnish points of attachment between the drug and the reacting compounds of the protoplasm.

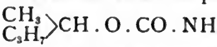
The synthetical hypnotics fall into three groups: (1) those containing halogens; (2) those containing alkyl groups and particularly the ethyl group; (3) those containing aldehydic or ketonic groups. Some hypnotics owe their soporific properties to a combination of these characteristics.

Isopral (trichloro*iso*propyl alcohol) is an example of an alcohol containing chlorine, recommended by the Bayer Company as a substitute for chloral hydrate. Isopral is more efficient than chloral and is freer from the depressing effects of the latter. Moreover, it is devoid of any cumulative action or unpleasant after-effects.

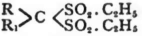
Diethylbarbituric acid (XXI), also known as *veronal*, may be regarded as an example of a hypnotic containing alkyl groups. It may be produced by condensing urea (carbamide) with either diethylmalonyl chloride or ethyl diethylmalonate, and many other methods of preparation are being patented even at the present time. Veronal is a colourless inodorous crystalline powder melting at 191°C, and dissolving in 12 parts of boiling and in 145 parts of cold water. It is a very satisfactory hypnotic and sedative, rapid in its action and free from untoward sequelæ; it has no disturbing effect on the heart or respiration. Fischer and Mering, who discovered veronal, have since suggested the employment of dipropylbarbituric acid under the name of *proponal*. This substance is also very rapid in its action, doses of 0·2 gram inducing sleep in from fifteen to forty minutes.



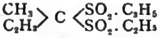
XXI.

Hedonal is a compound of comparatively simple structure  $\left.\begin{matrix}CH_3\\C_3H_7\end{matrix}\right>CH.O.CO.NH_2$ which is advocated by the Bayer Company as a safe soporific. Experiments have shown that this compound is completely oxidised in the system to water and carbonic acid, and it is accordingly quite devoid of any cumulative action. It is indicated in cases of sleeplessness due to mental strain or occurring in the course of neurasthenia or hysteria. When a prolonged use of hypnotics is required it serves as a useful alternative to the other soporifics.

There is an interesting class of hypnotics containing sulphur which illustrate the influence of the ethyl group in the development of the soporific effect. They are produced by the condensation of ethyl mercaptan, $C_2H_5.SH$, with a ketone, $RR^1:C:O$, whereby a mercaptol, $RR^1:C(S.C_2H_5)_2$, is produced, which is then oxidised to a disulphone XXII.


$\begin{matrix}R\\R_1\end{matrix}\!>C<\!\begin{matrix}SO_2.C_2H_5\\SO_2.C_2H_5\end{matrix}$

XXII.

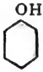

$\begin{matrix}CH_3\\C_2H_5\end{matrix}\!>C<\!\begin{matrix}SO_2.C_2H_5\\SO_2.C_2H_5\end{matrix}$

XXIII.

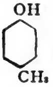
When acetone $(CH_3)_2C:O$ is employed in the condensation, *sulphonal* $(CH_3)_2C(SO_2.C_2H_5)_2$ is ultimately obtained; when diethyl ketone is used, *tetronal* $(C_2H_5)_2C(SO_2.C_2H_5)_2$ is the final product, whilst methyl ethyl ketone leads to the production of *trional* (Bayer). The hypnotic action increases with the number of ethyl groups, tetronal having the strongest narcotic effect. Trional, the intermediate member of the series, is, however, most often employed.

Antiseptics and Astringents

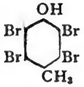
In considering the febrifuges, aniline was taken as the starting-point, and, in a discussion of antiseptics, phenol (carbolic acid, XXIV.) may be regarded as the prototype.



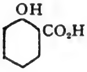
XXIV.



XXV.



XXVI.

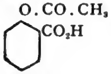


XXVII.

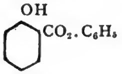
Phenol was, in fact, the first antiseptic recommended in surgical practice when it was employed in the original method of operation introduced by Lister. Although free from the destructive action exerted by aniline on the red corpuscles, phenol is a powerful irritant, and can only be administered internally in very small doses; in larger amounts it has a paralysing effect on the motor nerve-endings. The introduction of a methyl group into the nucleus as in para-cresol (XXV.) brings about a diminution in the poisonous character of phenol and at the same time increases the germicidal power of the substance. On this account the isomeric cresols (para-, meta-, and ortho-) are extensively used in disinfectants of the *lysol* type. The further substitution of halogen atoms for the hydrogen atoms of the benzene nucleus also greatly increases the germicidal efficacy of phenol and the cresols. Tetrabromo-para-cresol (XXVI.) and tetrabromo-ortho-cresol are among the most powerful of known germicides.

It has generally been found that the introduction of the acidic groups, carboxyl, CO_2H, and sulphonyl, SO_3H, diminishes very markedly the toxic action of a drug. Benzoic acid, $C_6H_5.CO_2H$, for example, is a substance producing only a very slight physiological effect. When a carboxyl group is introduced into the phenol molecule in a position contiguous to the hydroxyl group *salicylic acid* (XXVII.) is obtained. This product, in the form of its sodium salt, is a very important drug; it has a powerful antiseptic and germicidal effect, is free from the caustic property exhibited by phenol, and it has, moreover, a specific action in acute rheumatism. In its internal effect it greatly resembles quinine, even to the extent of producing a ringing in the ears and transient deafness. When there is toleration of the drug the exhibition of salicylic acid gives excellent results in the treatment of rheumatic troubles, but in certain cases the acid is apt to produce gastric disturbances, and to overcome this unpleasant effect various derivatives of salicylic acid have been put forward.

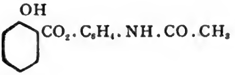
The well-known drug *aspirin*, acetylsalicylic acid (XXVIII.), is a good example of this series.



XXVIII.



XXIX.



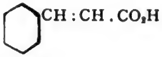
XXX.

Owing to its insolubility in the gastric juice it is devoid of the irritating action of salicylates on the stomach, but it is decomposed by the alkaline intestinal juices setting free salicylic acid. In order, however, that its action may be entirely beneficial it is important to bear in mind that alkalis of any kind should not be administered immediately after aspirin. A weak acid, such as citric acid, is, on the other hand, a useful adjuvant.

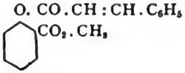
The *salols* are also employed to avoid the ill effects of salicylic acid on the stomach. They pass through this organ unchanged, and are then decomposed by the alkalis of the intestine. In these circumstances *salol* itself (XXIX.) is then hydrolysed into salicylic acid and phenol. As the latter substance may in the long run produce toxic effects, an improvement on salol has been made by the Bayer Company, who have brought forward the product acetyl-para-aminosalol (XXX.), or *salophen*. This substance, like salol, is insoluble in the gastric juice, but when hydrolysed in the intestine it furnishes salicylic acid and acetyl-para-aminophenol, an innocuous product like para-aminophenol itself (*see* p. 572), which is eliminated without further change.

Mesotan (Bayer Company), $HO.C_6H_4.CO_2.CH_2.OCH_3$, another drug of this class, is chiefly employed in external applications for the local treatment of rheumatic and gouty affections; it is used as a substitute for oil of wintergreen, and is free from the disagreeable properties of this substance.

Although benzoic acid is a comparatively inert substance, the introduction of a double linking between the carboxyl group, CO_2H, and the benzene nucleus leads to the formation of a more physiologically active compound, namely cinnamic acid (XXXI.).



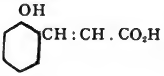
XXXI.



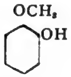
XXXII.

Drs. Jowett and Pyman, of the firm of Burroughs, Wellcome & Co., have endeavoured with success to combine the useful properties of salicylic and cinnamic acids in methyl cinnamylsalicylate (XXXII.), a compound which has been exhibited in rheumatism and allied conditions with excellent results, being tolerated in cases where aspirin has given rise to dyspeptic symptoms. When given with quinine it prevents the headache and other symptoms of quinism observed in those who are sensitive to this alkaloid. Cinnamic acid in the form of its sodium salt has been recommended in early cases of tuberculosis. When injected intravenously into animals it produces a marked increase in the number of white corpuscles, many of which assume a more active form, indicated by a more granular appearance of their protoplasm. This phenomenon is known as leucocytosis, and this increased activity of the leucocytes is an important factor in the combat incessantly waged by these cells, and more particularly their active polymorphonuclear forms, against the germs of disease. In Germany a dilute aqueous solution of sodium cinnamate is employed subcutaneously under the name of *hetol*. A solution of this salt in glycerine was suggested for the same purpose by the writer of this article in 1902. An 11 per cent. solution in this solvent is quite stable and free from any tendency to deposit crystals. The high temperature required for its production ensures its sterility, and its viscidity prevents a too rapid mixing of the solution with the blood stream, and thus promotes a more sustained local action. The physiological activity of cinnamic acid is undoubtedly due to its unsaturated ethylene linking, and in this connection it is interesting to notice that an even more unsaturated acid, namely, phenylpropiolic acid, $C_6H_5 . C \vdots C . CO_2H$, which contains a treble (acetylene) linking, has been used for laryngeal and pulmonary tuberculosis in the form of its sodium salt under the designation of *thermiol*.

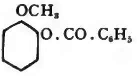
An extension of this cinnamate treatment to cases of malignant disease has led to the employment of substances combining the properties of salicylic and cinnamic acids, and the writer has suggested the use of the three isomeric coumaric acids. Of these isomerides the ortho-acid (XXXIII.)



XXXIII.



XXXIV.

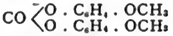


XXXV.

has given the most promising results, both clinically and in germicidal experiments *in vitro*.

The carbolic acid coefficients of germicidal value in respect of *Bacillus typhosus* estimated by the Rideal-Walker method are 6·5 for ortho-coumaric acid, 4·5 for the meta-acid, and 4·0 for the para-acid. These alkali coumarates and *tylmarine*, a preparation of the ortho-acid suitable for internal application, have been prepared by Messrs. Martindale.

Guaiacol, the monomethyl ether of ortho-dihydroxybenzene, a substance either obtained from beechwood tar or produced synthetically from ortho-anisidine, $CH_3O . C_6H_4 . NH_2$, is frequently indicated in tuberculosis, either free or in combination. *Benzosol*, prepared by Messrs. Meister, Lucius & Brüning, is guaiacol benzoate (XXXV.), which is split into guaiacol and benzoic acid in the intestine. *Duotal* and *creosotal*, prepared by the Bayer Company, are respectively the guaiacol (XXXVA) and creosol carbonates,



$$\mathrm{CO}\left\langle\begin{matrix}\mathrm{O\,.\,C_6H_4\,.\,OCH_3}\\ \mathrm{O\,.\,C_6H_4\,.\,OCH_3}\end{matrix}\right.$$

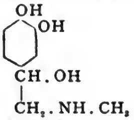
XXXVA.

which exert a favourable action on tuberculous conditions without irritating the stomach.

Synthetical Suprarenine

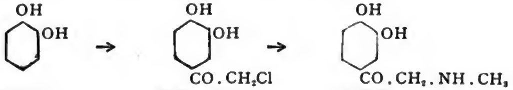
The synthetical medicaments described above have been employed as substitutes for the naturally occurring drugs, from which they generally differ entirely in chemical structure. The antipyretics of the phenacetin and antipyrin series have been used successfully as quinine substitutes, but nevertheless they do not resemble this alkaloid in chemical constitution. These differences are, moreover, not without their physiological counterpart, for in one respect at least the synthetical febrifuges differ from quinine, and that is in having no specific action in malaria, a malady in which the alkaloid exerts a well-defined beneficial influence. In this section an example of the successful synthesis of a naturally occurring drug will be discussed.

In 1901 Takamine and Aldrich, working independently, succeeded in isolating in a crystalline condition the active principle of the suprarenal capsules. This substance, which exerts an extremely potent influence in raising the blood-pressure, is the most powerful hæmostatic and astringent known. Its constitution was investigated by Von Fürth, Pauly, and Jowett; and in 1904 the last of these investigators indicated three formulæ for the base, stating that he considered that of these the following (XXXVI.) was the most probable:



XXXVI.

A compound having this constitution has since been synthesised by Messrs. Meister, Lucius & Brüning, which appears to have chemical and physiological properties identical with those of the naturally occurring base. In carrying out this synthesis, catechol (XXXVII.) (ortho-dihydroxybenzene) is treated with chloroacetic acid, $CH_2Cl.CO_2H$,



XXXVII. XXXVIII. XXXIX.

the resulting chloroacetylcatechol (XXXVIII.) is then allowed to interact with methylamine, whereby methylaminoacetylcatechol (XXXIX.) is produced. This substance when reduced is converted into synthetical suprarenine, XXXVI. This base, which is sold in the form of an aqueous solution of its hydrochloride with sodium chloride, can be obtained much more cheaply than the naturally occurring substance. It is, moreover, stable in these circumstances, whereas the natural product undergoes decomposition fairly rapidly. It may be pointed out in passing that this very active drug has received at least three different names—viz. *adrenaline*, *epinephrine*, and *suprarenine*.

IODOFORM SUBSTITUTES

Space does not admit of more than a brief reference to the synthetical products advocated as substituents for the powerful antiseptic, iodoform, CHI_3.

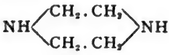
Isoform (Meister, Lucius & Brüning) is para-iodoxyanisole, $CH_3O.C_6H_4.IO_2$, a substance which is applied either as a dusting powder or in the form of paste; it is prepared from para-anisidine, $CH_3O.C_6H_4.NH_2$, by converting this base successively into its diazo-salt and then into para-iodoanisole, $CH_3O.C_6H_4I$. This product is treated with chlorine, the dichloride hydrolysed into the para-iodosoanisole, $CH_3O.C_6H_4.IO$, and then the last compound heated in steam, whereby equivalent proportions of para-iodoanisole and para-iodoxyanisole are obtained.

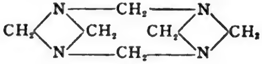
Aristol is an iodo-thymol, whereas *europhen* is isobutyl ortho-cresol iodide; both of these are recommended by the Bayer Company as iodoform substitutes.

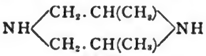
URIC ACID SOLVENTS

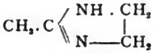
The treatment of gouty disorders with lithium salts has been almost superseded by the application of various synthetical bases, many of comparatively simple structure, which exercise a marked solvent action on uric acid.

Piperazine, or diethylenediamine (XL.): is prepared by the interaction of ammonia and ethylene dibromide; it is administered both in the free state and also in the form of its salts, such as the phosphate or tartrate. The internal application of piperazine is followed by an increased elimination of urates from the system, and it is accordingly indicated in cases of chronic gout. Dimethylpiperazine, XLII. (as the bitartrate, *lycetol*), has also been employed in this connection, and so also has *lysidine*, ethylene-ethenyldiamine (XLIII.), a base isomeric with piperazine, which in the form of its bitartrate is stated by Meister, Lucius & Brüning to dissolve eight times more uric acid than piperazine.

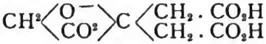

XL.


XLI.


XLII.


XLIII.

Hexamethylenetetramine (XLI.), the base produced by the interaction of formaldehyde and ammonia employed in the form of its salt with anhydromethylenecitric acid and even the sodium salt of this methylenecitric acid alone, have been employed in this connection, the former under the name of *helmitol*, the latter being termed *citarin*. Hexamethylenetetramine itself has found employment as a diuretic and solvent of uric acid concretions under the name of *urotropine*.



SYNTHETICAL DRUGS CONTAINING METALLIC OR METALLOIDAL ELEMENTS

There is a growing tendency to employ in therapeutics the organic derivatives of the metals and metalloids in preference to their inorganic compounds, as it not infrequently happens that in this way the element is more readily tolerated, and consequently can be administered with safety in larger doses.

For this reason mercury, copper, and silver salts of the organic acids are frequently employed both internally and externally. *Asterol*, a double salt composed of mercuric phenolsulphonate and ammonium tartrate, is stable in water, and neither precipitates albumin nor attacks metallic surgical instruments. Metallic salts of the organic acids are recommended as antiseptics. *Alumnol* is an aluminium β-naphthol-disulphonate put forward by Meister, Lucius & Brüning. *Nizin*, a zinc salt of sulphanilic acid $(NH_2 . C_6H_4 . SO_3)_2Zn.7H_2O$, is recommended by Messrs. Burroughs, Wellcome & Co. as a non-irritating, non-toxic antiseptic, which even in strong solutions does not coagulate albumin.

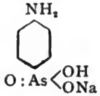
Copper cinnamate (*cuprocitral*) has been used in the form of an ointment in ophthalmic work. Strontium cinnamate has been tried in connection with the treatment of tuberculosis already mentioned.

Bismuth salicylate and bismuth cerous salicylate have been employed in intestinal troubles, whilst bismuth subgallate finds employment as a non-irritant antiseptic dusting powder, under the name of *dermatol.*

Arsenic furnishes a good example of an element which is much more readily tolerated in the form of an organic salt. For this purpose sodium dimethylarsinate

$$(CH_3)_2 AsO . ONa, 3H_2O$$

was formerly advocated, as it is less poisonous than Fowler's solution (potassium arsenite). The use of this substance is, however, attended with one disadvantage—namely, the production in the system of malodorous cacodyl derivatives. A much more satisfactory vehicle for the therapeutic application of arsenic has been found in the substance known commercially as *atoxyl*, and which is prepared in a crystallised form by Messrs. Poulenc Frères and also by Messrs. Burroughs, Wellcome & Co. This compound was originally obtained by Béchamp in 1863 by heating aniline arsenate at 190–200° C., whereby a substance was formed which he considered was an anilide of arsenic acid, $C_6H_5 . NHAsO(OH)_2$. On neutralising this substance with sodium hydroxide a soluble crystallisable salt was obtained which was supposed by Béchamp, and more recently by Fourneau (1907), to have the constitution $C_6H_5 . NH . AsO(OH) . ONa$, together with some water of crystallisation. The properties of the salt do not, however, correspond satisfactorily with this formula, and since the compound has come into use as a drug its constitution has been revised by Ehrlich & Bertheim. Their results, published in the *Berichte der deutschen chemischen Gesellschaft* for July 20th, 1907, show that in reality the substance is a salt of para-aminophenylarsinic acid having the following graphical formula—



and the commercial product generally contains four molecules of water of crystallisation. By analogy with sulphanilic acid, $NH_2 . C_6H_4 . SO_2 . OH$, the free acid has been called arsanilic acid, $NH_2 . C_6H_4 . AsO(OH)_2$, and accordingly atoxyl may be termed sodium arsanilate, $NH_2 . C_6H_4 . AsO(OH)ONa, 4H_2O$. In this substance, the arsenic is very tenaciously held by the organic radicle, and is split off only under the influence of fused potash or by the action of hot hydriodic acid. The strength of the connection between the arsenic and phenyl is probably correlated in some way with the therapeutic action of the salt, for it has been found that atoxyl is forty times less poisonous than Fowler's solution. The salt may be applied either internally or externally; it has been indicated in several maladies, among others in tuberculosis and various skin troubles. Of special interest at the present time are the promising results which have attended the use of atoxyl in cases of sleeping sickness. Although it is as yet too soon to claim any specific action for the drug in this or other diseases, yet it is already evident that in this organic arsenic derivative we have a valuable therapeutic agent.

Although this review of the modern synthetical drugs is unavoidably brief and incomplete, it is hoped that it will serve to throw some light on the chemical nature of these substances many of which are at present in everyday use.

THE ELECTROLYTIC REDUCTION OF ORGANIC SUBSTANCES

BY PERCY A. HOUSEMAN, PH.D. (WÜRZ.), A.I.C.

ORGANIC substances capable of electrolytic reduction may be divided into two classes: (1) easily reducible substances, *i.e.* those which are reduced at any cathode; (2) difficultly reducible substances—those which are reduced only at cathodes possessing a particularly high "super-tension," limited practically to cathodes of lead and mercury. These two classes will be considered separately.

The method, briefly outlined, consists in allowing the hydrogen evolved from the cathode to act upon the organic substance, which is dissolved in a suitable solvent—usually sulphuric acid or aqueous or alcoholic alkali. The substance does not need to be an electrolyte, for the action is a purely chemical reduction by the hydrogen liberated at the cathode. Different chemical agents often lead a reduction in different directions, or arrest the same at different phases; and in the electrolytic process this finds a parallel in the regulation of the course of the reduction by variations in the cathode material—current strength, and, in the case of easily reducible substances, more particularly by the potential,[1] which regulates the pressure under which the ions are discharged from the solution, *i.e.* the energy with which the liberated hydrogen is capable of reacting. A higher potential corresponds in action to the use of a stronger chemical reducing agent.

In a similar way, choice of the size of the electrodes gives the power of regulating the concentration of the discharged ions, *i.e.* the number of ions liberated per unit of cathode surface, this factor also influencing the course of electrolytic reductions.

The earlier work was done on easily reducible substances by

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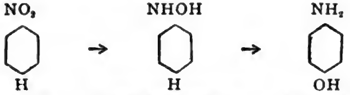
[1] Haber, *Zeitschr. f. Electroc.* 4 (1898), 506; *Zeitschr. f. phys. Chem.* 32 (1900), 193.

Gattermann, Elbs, Haber, Häussermann, Löb, and others. All these investigators paid special attention to the electro-reduction of the nitro- (NO_2) group in aromatic compounds—in particular nitrobenzene—both as a preparative method and also from a purely physical standpoint.

The first experiments on electro-reduction (as well as electro-oxidation) of organic substances were made between 1875 and 1886 by Goppelsroeder,[1] who worked on the production and bleaching of dyestuffs by means of electrolytically produced hydrogen and oxygen. From aniline sulphate by electro-oxidation Goppelsroeder obtained aniline-black, while potassium thiocyanate on electrolytic reduction yielded the dye canarin.

More important, both practically and theoretically, was the work of Gattermann on the electro-reduction of nitrobenzene and its derivatives. The chemical reduction of this substance yields, according to the reducing agent employed, azoxybenzene, azobenzene, hydrazobenzene, aniline, and benzidine. All of these products may also be obtained with the help of the electric current, variations in the conditions of electrolysis corresponding, as noted above, to the use of different chemical reducing agents.[2]

Gattermann,[3] however, and independently Clement and Noyes,[4] succeeded in obtaining an electro-reduction product of nitrobenzene, which all chemical agents had failed to yield, viz. para-amido-phenol. As an intermediate product phenyl-hydroxylamine is formed, subsequently undergoing transformation to amido-phenol, thus:



Nitrobenzene. Phenyl-hydroxylamine. Amidophenol.

Corresponding amidophenols were obtained under similar conditions from other aromatic nitro-compounds, such as nitrotoluene, dinitrobenzenes, etc. When nitrobenzene is reduced in alcoholic alkaline solution, the chief products are the azo- and azoxy-compounds, while in acid solution the reduction is carried further, and the hydrazo- and amino-compounds are chiefly formed. This difference in the phase to which nitrobenzene is reduced in alkaline and acid solution, Löb ascribes, in the case of an alkaline solution, to the liberated sodium causing the reduction rather than the nascent hydrogen.[1]

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[1] Oesterreich's *Wollen und Leinen Industrie*, Reichenberg, 1885.

[2] See scheme on p. 592.

[3] *Ber. der. deut. chem. Gesell.* 26 (1893), 1849.

[4] *Ibid.* 990.

Häussermann[2] was the first to obtain benzidine—

$$NH_2 - C_6H_4 - C_6H_4 - NH_2$$

as an electro-reduction product of nitrobenzene, Löb[3] subsequently obtaining benzidine in excellent yield by reducing first to the azo-phase in alkaline solution, and completing the reduction in dilute sulphuric acid solution. Löb also reduced many derivatives of nitrobenzene, such as the nitrobenzoic acids.

The first attempt to follow these electro-reduction processes quantitatively was made by Elbs,[4] who showed that the reducibility of nitro-compounds diminished as the number of nitro groups is increased. The quantitative investigation of these processes was, however, much more fully worked out by Tafel for difficultly reducible substances, and is described later.

Löb[5] called attention to the effect of different kinds of cathodes on the reduction of nitrobenzene, a factor which is of primary importance with difficultly reducible substances. Thus tin and copper electrodes yielded more aniline, nickel more azoxybenzene. Elbs[6] also showed that under otherwise equal conditions, nitrobenzene was more quickly reduced at a lead cathode yielding more aniline, than at a platinum cathode, at which more amidophenol was produced.

The following scheme shows at a glance the different reduction products which nitrobenzene has yielded, the reduction of this substance, and of its derivatives, by means of the electric current, having been of considerable theoretical and practical importance.

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[1] Löb, *Zeitschr. f. Electroc.* 2 (1896), 529.

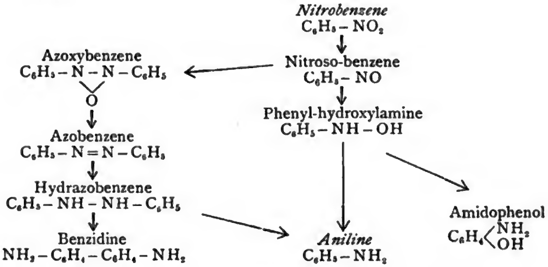
[2] *Chem.-Ztg.* 17 (129).

[3] *Zeitschr. f. phys. Chem.* 34 (1900), 641; *Zeitschr. f. Electroc.* 7 (1900), 320.

[4] *Journ. f. prak. Chem.* 43 (1891), 39.

[5] *Zeitschr. f. Electroc.* 4, 430; Löb and Moore, *Zeit. f. phys. Chem.* 47 (1904), 418.

[6] *Zeitschr. f. Electroc.* 2, 472.



We turn now to the second class—the electrolytic reduction of *difficultly* reducible substances. This subject is a more recent one. The first such reduction was carried out by Tafel[1] on strychnine in 1898, to be followed in rapid succession by a large number of other compounds, so that the method has become one of great importance not only as a preparative method, but also in view of the many physico-chemical problems involved.

The advantages of the electro-reduction of organic substances—more particularly of difficultly reducible substances—will be considered briefly at the conclusion of the article.

A short description of the method and apparatus employed by Tafel for the quantitative investigation of these reductions must now be given.[2] Experiments must be made on a small scale to see firstly if the substance is capable of being electrolytically reduced at all, and secondly to determine the influence on the time required for the reduction of variations of current concentration,[3] current density,[4] etc. The time required is an important factor, as many of the products obtained are easily decomposable. Such preliminary experiments are made in the closed apparatus shown in fig. 1.

The lead beaker (A) serves as anode. The porous cell (B) separates anode chamber from cathode chamber. The cathode chamber is closed by a well-fitting trebly bored rubber stopper, the centre hole of which carries the solid lead cathode (C), while the other holes are fitted with a thermometer (T) and a tube (D) for leading off the evolved hydrogen.

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[1] *Annalen*, 301 (1898), 285.

[2] *Ber. d. deut. chem. Gesell.* 33 (1900), 2209; *Zeitschr. f. phys. Chem.* 34 (1900), 187.

[3] Current concentration = current per litre of cathode liquid.

[4] Current density = current per square centimetre of cathode surface.

Connected in the same circuit is a second exactly similar apparatus, which contains sulphuric acid only, and *no* organic substance.

The evolved hydrogen from each cell is collected from time to time in a specially constructed pneumatic trough during a period of one minute. The difference in the two volumes (*v-h*) shows how much hydrogen has been used up by the process of reduction, and is a direct measure of the course of the reduction at that moment.

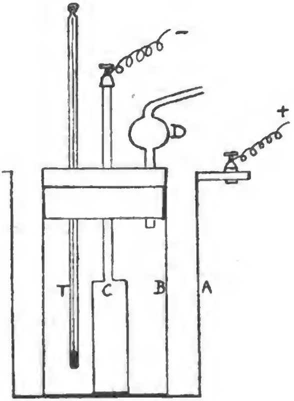

FIG. 1.

If this difference (*v-h*) is graphically plotted against time, a curve of the velocity of reaction is obtained. Fig. 2 shows a typical curve taken in this case for caffeine. It will be seen that the volume of hydrogen used diminishes regularly with the amount of unreduced substance remaining in the solution. One great advantage which such curves possess is that the area enclosed by the curve and the axes OA·OB is a measure of the total hydrogen used for the reduction. A comparison between the total hydrogen used and that theoretically required by an equation gives valuable assistance in following the course of the reduction and in knowing what products may be expected. Thus, from the curve in fig. 2 the enclosed area when measured up represents a volume of 2,250 cc. while the equation

$$\underset{\text{Caffeine}}{C_8H_{10}O_2N_4} + 4H = \underset{\text{Desoxycaffeine}}{C_8H_{12}ON_4} + H_2O$$

requires (for 10 grams of caffeine) 2,303 cc. hydrogen—the difference between the observed and calculated amounts being well within the limits of experimental error.

It has already been mentioned that the cathode material affects the reduction of aromatic nitro-compounds. With difficultly reducible substances, such as caffeine and uric acid, a reduction at any other cathode than mercury or lead is seldom possible.

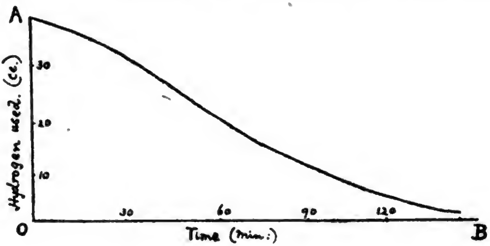

FIG. 2.

The cause of this important fact is that the hydrogen from a lead cathode is evolved at a higher potential, and therefore possesses greater energy than the hydrogen evolved, say from a platinum cathode. This is intimately connected with the high "super-tension" of lead. Caspari[1] showed that the tension at various cathodes at which gaseous hydrogen visibly escapes differs widely. For lead and mercury this tension is highest—for platinum lowest. The excess of potential over that of a reversibly working hydrogen-oxygen-sulphuric acid element Caspari called the "super-tension" of the metal in question. The following are the values for the "super-tension" of a few metals:

Mercury 0·78 volt.	Lead 0·64.	Copper 0·23.
Silver 0·15.	Gold 0·02.	Platinum 0·005.

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[1] Caspari, *Zeitschr. f. phys. Chem.* 30 (1899), 89.

It is this property of rendering difficult the escape of the hydrogen, which lead and mercury possess in such high degree, that allows the reduction of these difficultly reducible organic substances to be accomplished—while at all other cathodes they remain unaffected.

Quantitative experiments such as those already described show that the time required for the reduction is least by using a small current *density* (*i.e.* a large cathode) and as high a current *strength* as is compatible with holding the temperature within the necessary limits. When working on a larger scale, cooling (by means of hollow electrodes) is usually necessary.

One of the most interesting phenomena connected with this subject, and one which is also intimately correlated with "super-tension," is the poisonous influence of traces of foreign metals in the cathode chamber. Tafel[1] has shown that ·004 milligram of platinum per ten square centimetres of cathode surface is sufficient to bring the reduction to a standstill immediately. The other enemies of electro-reduction arranged in order are, after platinum, silver, tin, copper, mercury, zinc, and iron; though none approach platinum in its efficacy in causing the "spontaneous depression" of the reduction.

The most obvious explanation of this action is that the platinum is electrolytically precipitated on the surface of the cathode, and that then one is dealing virtually with a platinum cathode, which, as has been already shown, by reason of its low super-tension, *i.e.* the ease with which it allows the hydrogen to escape as gas, does not permit of the reduction being accomplished. Tafel's[2] extensive researches on this problem show that, not only is the amount of platinum present far too minute to form even the thinnest possible skin on the surface of the cathode, but also the action is different on different cathodes, and further, gold, which has almost as low a super-tension as platinum, should have quantitatively almost as great a disturbing effect, whereas gold is not nearly so poisonous to a lead cathode as platinum.

The conclusion is drawn that the platinum must exercise a catalytic influence on the surface of the cathode material. The disturbing action of minute traces of platinum and other metals has been one of the great difficulties in the application of

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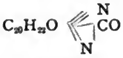
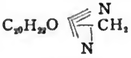
[1] *Zeitschr. f. phys. Chem.* 34 (1900), 187-228.

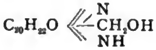
[2] Tafel and Emmert, *Ibid.* 52 (1905), 349.

Tafel's electro-reduction process as a preparative method, though the physical researches to which he was thereby forced have revealed much that is theoretically of considerable importance.

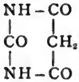
The electric current has been most prolific in the preparation of products which cannot be obtained by other reducing agents. A few of these may be mentioned as typical examples: Strychnine,[1] the first of these substances to be submitted to electrolytic reduction, yielded strychnidine and tetrahydrostrychnine, both these substances possessing in a less degree the same physiological action as strychnine.

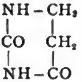

Strychnine.

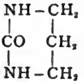

Strychnidine.


Tetra-hydro-strychnine

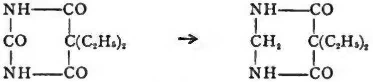
As an example from the ureides, barbituric acid[2] may be cited, this substance yielding on reduction a mixture of hydrouracil and trimethylene-urea.


Barbituric acid


Hydro-uracil


Trimethylene urea

The behaviour of di-ethyl-barbituric acid,[3] which is now being used somewhat extensively as a soporific under the name of Veronal, is very remarkable. Instead of being reduced in a manner analogous to barbituric acid, the hydrogen attacks the urea residue thus:—



Up to the present this is the only observed instance in which the carbonyl (CO) group of the urea chain has been electrolytically reduced.

Of particular interest are the electro-reduction products of uric acid,[4] inasmuch as this physiologically important body has not been directly reduced by any other means, if one leaves out of account the breaking down of the molecule by hydriodic acid. Three substances are obtained by the electrolytic reduction of uric acid—puron, isopuron, and tetra-hydro-uric acid. The manner in which the hydrogen is added on is seen clearly from the following formulæ.

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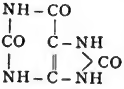
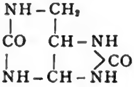
[1] *Annalen*, 301 (1898), 285.

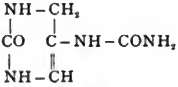
[2] *Ber. d. deut. chem. Gesell.* 33 (1900), 3383.

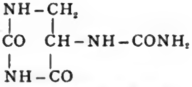
[3] Tafel and Thompson, *Ber. d. deut. chem. Gesell.* 40 (1907), in press.

[4] *Ibid.* 34 (1901), 258.


Uric acid


Puron


Isopuron[1]


Tetra-hydro-uric acid

It will be noticed that puron and isopuron are isomeric, *i.e.* they possess the same empirical formula, $C_5H_8O_2N_4$. The former is transformed to the latter by treatment with caustic alkali.

The methyl derivatives of uric acid[2] also yield a series of corresponding methyl derivatives of puron and isopuron. In no case, however, is a substance corresponding to tetra-hydro-uric acid produced.

The slightly higher super-tension of mercury than lead is the cause of some substances being reduced better with a cathode of the former metal than with one of the latter.[3] Examples are acetone and caffeine. In the case of camphor no reduction whatever takes place at a lead cathode, while, with a mercury cathode, borneol is obtained in good yield.

It is to be expected that the electric current will come more and more into use as a preparative method for the reduction of organic substances. By varying the potential one can, as Nernst expresses it, produce pressures whose amount varies between very small fractions of an atmosphere, and many million atmospheres; and this is the reason why the electric current accomplishes the reduction of some substances, such as uric acid, which remain entirely unaffected by the ordinary chemical reducing agents.

The successful clearing away of the many preliminary difficulties leaves the method a well-understood and comparatively simple one, besides which, electro-reduction possesses the further advantage of the absence of other reagents, which usually entail a more or less troublesome process of elimination in the course of reduction by the usual chemical agents.

[1] Tafel and Houseman, *Ber. d. deut. chem. Gesell.* 40 (1907), 3743 (in press). Houseman, *Dissertation*, Würzburg, 1906.

[2] *Ber. d. deut. chem. Gesell.* 34 (1901), 279.

[3] Tafel and Schmitz, *Zeitschr. f. Electroc.* 8 (1902), 280.

DIFFUSION AND ENTROPY OF GASES

BY S. H. BURBURY, F.R.S.

1. THIS subject has been treated by Lord Rayleigh in *Phil. Mag.* January—June 1875, under the title "On the Work that may be gained by the Mixture of Gases," pp. 311, 318, and by Prof. Bryan in his recent work on *Thermodynamics* (Leipzig: Teubner). Each writer's work presents some difficulties, which I propose to consider in the present paper. Rayleigh's argument is based on the fact that hydrogen escapes through fine apertures more rapidly than air, even at greater pressure, enters to supply its place. His conclusion is that "the work that may be done in the mixing of volumes v_1 and v_2 of two different gases is the same as would be gained in the expansion into vacuum of the first gas from volume v_1 to $v_1 + v_2$, together with that which would be gained by the expansion into vacuum of the second gas from volume v_2 to $v_1 + v_2$." It is understood that the gases follow the law of independent pressures, each behaving as a vacuum to the other. The law is thus stated with complete generality, and without qualification as to the nature of the containing materials or otherwise. Bryan states the law in substantially the same form at p. 125 of his work. I therefore call it the Rayleigh-Bryan law.

2. The thing to be proved, as I understand it, is this: that two physically different gases, if separated, can be made to do mechanical work, at the expense, of course, of their heat, in mixing; on the other hand, if they mix by diffusion, no work is done. Therefore by allowing them to mix by diffusion, we lose the opportunity of converting heat into work, *i.e.* we lose the "available energy" which they had by virtue of their separation.

3. Before discussing the arguments in detail, it will be well to calculate the work that can be done in case of two gases, one of which is hydrogen, in a cylinder of volume 2v, separated, as Rayleigh suggests, by a piston porous to the hydrogen, but hypothetically impermeable to the other gas, say oxygen. They

are supposed to be both at the same pressure, p, and the same temperature, and each initially occupying volume v. Also the temperature is maintained constant notwithstanding the conversion of heat into work during expansion of either gas. The piston being fixed, hydrogen escapes through it, until it is of the same density throughout the cylinder, oxygen behaving as a vacuum to it. This being done, the pressure is $\frac{3p}{2}$ on the oxygen side, and $\frac{p}{2}$ on the hydrogen side. The piston being now set free, the oxygen expands, and if its expansion takes place very slowly, the hydrogen, as it can pass through, will be throughout the process at the same pressure on either side of the piston. The work done by expansion of the oxygen is then the same as if the hydrogen were absent, and is

$$\int_0^v \frac{pv}{v+x}\,dx = pv \log 2.$$

It is therefore exactly half the work required by the Rayleigh-Bryan law. At the end of the process the two gases are uniformly mixed throughout the volume 2v of the cylinder. No further work can be obtained from the system while it is in that state. If the piston, instead of being impermeable to oxygen, were permeable by it, only in less degree than by hydrogen, the work obtained would be less—that is, less than half the work required by the law.

4. We must now consider Rayleigh's arguments. They seem designed to show that the separation of mixed gases generally involves the expenditure of work, and that this work may be regained in their mixture. In his first example a mixture of steam and hydrogen under a piston in a cylinder of volume v is compressed, the temperature being maintained constant, until at volume v_1, the saturation point of the steam is reached, and it begins to liquefy, and is all liquefied at volume v_0. I understand Rayleigh to say that at this point all the hydrogen exists as gas between the water and the piston, none being held in solution by the water. The water is then put in a separate vessel, and is evaporated and expanded to its original volume and temperature. The hydrogen also expands to its original volume and temperature. The work gained in expansion is, he says, equal to that spent in compres-

sion, so that in the complete cycle, the whole system being restored to its original state but for the separation of the gases, no work on the whole is done. Does this result support Rayleigh's doctrine? It is true work is spent during the separation, and gained during the subsequent expansion—that is, the gases when separated have available energy. But this is not because they are separated, but because they are compressed, and they would have precisely the same available energy if they were not separated at all, but expanded as a mixture to their original state.

5. In his second example Rayleigh shows how the separation of two gases may in a certain case, and doubtless in other cases, be effected by chemical means.

6. In the third argument (p. 313, etc.), Rayleigh considers the case in which two gases, a heavier and a lighter, say oxygen and hydrogen, are partially separated by the action of gravity in a vertical tube. Suppose them to have arrived at a state of equilibrium, and the partial pressures at the base of the tube are the same as those of the same two gases mixed in a reservoir, so that if the tube communicates with the reservoir at its base no oxygen or hydrogen escapes from or to the reservoir. Rayleigh proves that if the mixture of gases in each element of the tube be separately compressed to the total pressure at the base, and is then brought down to the level of the base, the work spent in the compression exceeds in the case of two gases that gained from gravity in the descent. Were only one gas present, it would be equal to the work gained.

7. In order to make the cycle complete, except that at the end the gases are partially separated, at the beginning uniformly mixed, I will work out the problem independently. As will be seen, I shall obtain Rayleigh's result above stated. I consider two cases:

Case I.—A single gas is at uniform pressure and temperature in a horizontal tube ACB of length S. C is the middle point, and initially the centre of gravity of the gases. I avail myself of the permission given by Rayleigh (p. 318, line 3) to divide the tube into elements of length, and to insert between each pair of successive elements a piston, fixed or movable, to prevent passage of molecules from one element to another, also permission to remove such pistons. Then—

Process (1). Fix the pistons and turn the tube about the end

A into the vertical position. In that we spend work MgAC, if M be the mass of the gas. We need not take into account the mass of the tube.

Process (2). Set the pistons free, then compression ensues towards the base. The centre of gravity falls to C_1. We gain work from gravity MgC_1C, which is all spent in the compression.

Process (3). Again fix the pistons, and turn the tube about A into the horizontal position. In that we gain work $MgAC_1$.

Process (4). Let the gas expand till it reaches its initial uniform density. In that we gain work by the expansion equal to the work spent in compression, that is MgC_1C.

In all we have spent work MgAC in (1) and gained work $MgAC_1$ in (3) and MgC_1C in (4)—that is, we have spent zero work.

8. *Case II.*—Instead of a single gas, let there be in the horizontal tube equal numbers of molecules of oxygen and hydrogen uniformly mixed, then insert and fix the pistons, and perform Process (1) as before. In that we spend work MgAC as before, M being the combined mass of the gases.

Process (2). Set the pistons free, and compression takes place as before. The c g falls to C′, and the work of compression, which is done by gravity, is MgCC′.

Before Process (3) we must now interpolate a new process (2A)—namely, remove the pistons, so that diffusion takes place. The gases assume a new position of equilibrium, in which each behaves as a vacuum to the other.

If R_1 denote the density per unit of volume for oxygen at the base, r_1 its density at height s, and if R_2, r_2 be the corresponding densities of hydrogen, $r_1 = R_1e^{-2hm_1gs}$, and $r_2 = R_2e^{-2hm_2gs}$, m_1 being the mass of a molecule of oxygen, m_2 that of hydrogen—that is, oxygen partially replaces hydrogen in the lower, hydrogen replaces oxygen in the upper strata. The centre of gravity falls to C″. Before considering what becomes of the work thus gained MgC′C″, let us perform Processes (3) and (4). Fix the pistons, Process (3), and turn the tube about A into the horizontal position. In that we gain work MgAC″.

Up to this point we have spent work MgAC, and gained MgAC″.

Then Process (4), set free the pistons, and let the gases expand without diffusion till they attain uniform pressure, but not uniform mixture, throughout the tube. The work gained in that expansion is equal to the work spent by gravity in the compression. If, then, the work gained from gravity in Process 2A, namely MgC″C′, is all spent in compression, there is in the complete cycle zero work spent.

But if, as I think is the case, part only of the work MgC″C′ is spent in compression, and part converted into heat, *i.e.* dissipated (see Raleigh's remarks, pp. 317-8), we have in the whole spent work equivalent to the dissipated energy.

9. Is not the theory this? If we had suitable machinery to act on individual molecules, *e.g.* if we could employ Maxwell's demons for the purpose, we might effect the separation of the oxygen and hydrogen molecules mixed in the horizontal tube without doing any work, no work being *essential* to the process, unless molecules of the same gas appreciably attract or repel each other, which is understood not to be the case. As we have no such machinery, and cannot employ the demons, we have to effect the separation by indirect processes, as in the example given. And these indirect processes generally involve dissipation. Work is spent in the separation of the gases, but the energy is in no sense available. Energy dissipated is unavailable.

PROFESSOR BRYAN'S ARGUMENT

10. I come now to Prof. Bryan's argument, which is mainly theoretical. I will give his proof of the law (for there is a logical proof) as I understand it. I begin with his definition of "entropy," the second of p. 58.

(*a*) If the unavailable energy of any system receives any positive or negative increase δQ, the entropy is increased by $\frac{\delta Q}{T_0}$, T_0 being the lowest available temperature. I think we may say, at least by way of example, without affecting the generality of this definition, that δQ is the heat which passes into the refrigerator in the lower isothermal of a Carnot cycle in which the system is the working substance.

(*b*) This being the definition of entropy, it follows that if the entropy increases, the unavailable energy increases. Therefore, since energy is either available or unavailable, if while the entropy increases no energy enters or leaves the system from or to external bodies, the available energy diminishes.

(*c*) The entropy of a system is a function of the physical state of the system, and cannot change while that state remains unchanged. Therefore, if the system be a gas, at all events if a perfect gas, it may be expressed as a function of the temperature and volume—and, it may be, also a function of the number, n, of molecules in the given volume, say generally it is $f(n, T, v)$.

(*d*) But, if the gas be the working substance in a Carnot cycle, the heat drawn from the reservoir in an isothermal expansion from volume v to volume $v + \delta v$ is proportional to the pressure, that is, for given v, proportional to n. Therefore, also, the heat δQ, which passes into the refrigerator in the same cycle, is proportional to n. Therefore, if S_n be the entropy of a single gas containing n molecules in volume v, $S_{n'}$ the entropy for the same gas containing n′ molecules in volume v, $\frac{\delta S_n}{\delta S_{n'}} = \frac{n}{n'}$. And since S_n and $S_{n'}$ cannot differ by a constant, $\frac{S_n}{S_{n'}} = \frac{n}{n'}$. That is, $\frac{f(n, T, v)}{f(n', T, v)} = \frac{n}{n'}$, for all values of n and n′. This requires that $f(n, T, v) = n\phi(T, v)$, where $\phi(T, v)$ denotes some function of T and v. Therefore $f\,\overline{(n + n'}, T, v) = (n + n')\,\phi(T, v) = n\phi(T, v) + n'\phi(T, v)$, or the entropy of a single gas, in volume v, is the sum of the entropies of all the parts into which it may be conceived as divided, provided that each part is free to move throughout the whole of v, and is not confined by partition to a part of v. (N.B.—This is my own argument, and not Bryan's. It would not necessarily apply to two different gases, because the physical state of each might be affected by the presence of the other.) Bryan, however, proves the same thing for two gases as follows:

(*e*) The entropy of a gas occupying volume v is the same whether it has that volume all to itself, or shares it with another gas at the same temperature and pressure. In other words each gas is in respect of its entropy a vacuum to the other. *Query*, is there any limit to this law as the density increases?

A proof of this is given at p. 124 by the following method, which I understand to be founded on experiment. Given a mixture of two gases in cylinder of volume 2v, each having the same partial pressure ½p, and the mixture having combined pressure p, the mixture is cooled until the gases liquefy, one before the other. The liquids are put in separate vessels, and evaporated, and heated until each occupies volume 2v, and is at the original temperature of the mixture. It is assumed (1) that the volumes of the liquids are negligible in comparison with their vapours; (2) that the specific heats are constant; (3) that the latent heat of evaporation of either component is unaffected by the presence or absence of the other. On these assumptions Bryan concludes that the process is reversible. Therefore entropy is the same at the end, when each gas has a volume 2v to itself, as at the beginning, when they had one volume 2v in common, *cæteris paribus*.

(*f*) The entropy of a gas in volume v increases, *cæteris paribus*, when v increases. This follows from the definition (*a*). For S denoting entropy, $\delta S = \frac{\delta Q}{T_0}$; therefore $\frac{dS}{dv} = \frac{1}{T_0}\frac{dQ}{dv}$, and $\frac{dQ}{dv}$ is always positive by the Carnot cycle.

11. We may now compare two states of a system: state A, two gases occupying each a volume v, separated by a partition, and each at pressure p, and temperature T; state B, the same two gases mixed in volume 2v, *cæteris paribus*. Each gas has in state A entropy $n\phi$ (T, v), and by (*e*) it has in state B entropy $n\phi$ (T, 2v), which by (*f*) is greater than $n\phi$ (T,v)—that is, each has greater entropy, and therefore the system has greater entropy in B than in A. Therefore the system has less available energy in B than in A, or available energy is lost in the process of mixing, no energy passing in that process from or to external bodies.

12. Evidently the amount of available energy that each gas loses in the process of mixing is measured by the entropy that it gains—that is, the difference of entropy between the gas occupying volume v, and the same gas *cæteris paribus* occupying volume 2v—that is, the available energy lost by the process is for each gas the available energy it would lose by expanding into vacuum from volume v to volume 2v, the temperature being constant. The Rayleigh-Bryan law is thus formally and completely proved in the sense of Bryan's definition of available energy, whatever that may be.

13. I note that Bryan's process of separating the gases (p. 124) involves no expenditure of work. If, therefore, the gases when separated have more available energy than when mixed, it is not because work has been spent in their separation which can be regained in their mixture, in which Bryan seems to differ from Rayleigh.

14. The argument (Bryan's) seems to prove too much, if I am right in (*d*) above. For if so, the argument applies equally to two portions of any single gas. Therefore, we could increase the available energy of a single gas by dividing it into two parts by a partition. Even if (*d*) be not accepted, does not the same thing follow from Bryan's proof (*e*) applied to two portions of the same gas? It is true that this process, although it separates two gases having different temperatures of liquefaction, cannot separate two portions of the same gas. But we may separate the two portions, and put them in separate vessels, immediately after or before liquefaction, and then evaporate them separately, till each attains its original temperature and original volume 2v. If the process is reversible for two gases, is it not equally reversible for two portions of the same gas? If so, then two portions of the same gas, each at the same temperature and pressure, mixed in one volume 2v, have more entropy than they would have if they each occupied volume v, and were separated by a partition.

15. Subject to the doubt raised in 14, the argument of arts. 10 and 11 seems logically conclusive, that two separated gases lose available energy, whatever that may mean, when allowed to mix by diffusion, and that the amount of available energy lost is that stated in the Rayleigh-Bryan law.

16. Nevertheless, it does not necessarily follow that the available energy lost is *the practical possibility* of transforming heat into work. For the only definition of available energy which we have used in the argument is that it diminishes with increase of entropy. In fact, if the entropy is a function of T and v, and independent of any conditions, the available energy must be a function of T and v, and independent of any conditions. It does not, therefore, follow that because a system loses available energy in passing from state A to state B, therefore we can actually transform heat into work given the system in state A. It may be that in state A work is *theoretically*, but owing to the external conditions not *practically*, derivable from the system. In Bryan's definition of available energy (p. 43) "work theoretically derivable" must mean "work which under suitable external conditions might be derived." If two separated gases (state A) are each at pressure p, and are surrounded by infinite air at pressure p and at the same temperature as the gases, no part of the heat of either gas can

be transformed into work while the whole system is what it is. We then call upon the experimental philosopher to convert it into something that at present it is not, but without initially altering its entropy. This he can do by substituting for the partition separating the gases a piston porous to one, but not, or not in the same degree, porous to the other. We might say paradoxically that, while the separated gases are separated, the available energy is not available; but when by using the porous piston the separated gases are not separated, the available energy, or some part of it, is available. A dinner is placed before Tantalus, and it is mathematically proved to him that it is an available dinner, but he is unable to eat or drink.

17. There may be other transformations of the system which would admit of work being obtained. One other method has been suggested—namely, a liquid which absorbs one of the two gases, but not the other. By such a liquid we might perhaps reduce one of the two gases to lower pressure than the other, and so render the performance of work possible. But that method might be applied with equal success to two separated portions of a single gas.

18. Bryan uses instead of the porous piston a membrane (p. 125). And he suggests the ideal case of two membranes, one of which is porous to gas (1), but wholly impermeable to gas (2), the other membrane *vice versa*. But should not this ideal combination of gases and membranes be required to prove its own existence before it is used to prove anything else? If Bryan says it does exist, I accept his authority.

19. Another line of argument to prove the Rayleigh-Bryan law, not expressly relied upon by Bryan, is as follows: If any irreversible process takes place in the interior of a system, the unavailable energy of the system, and therefore the entropy, is increased. And the mixture by diffusion of two gases originally separated is stated by Bryan to be an irreversible process. I admit the argument, if the diffusion is an irreversible process. But there is no proof that it is not a periodic process.

20. It is, of course, a familiar experience that two separated gases, each at the same pressure and temperature, if the partition be removed, at once begin to mix—or, let us say, if they are originally mixed in different proportions on the two sides of the partition, at once begin to assume a more uniform mixture. But

that phenomenon is as consistent with the motion being periodic as with its being asymptotic—*i.e.* irreversible. For if periodic, any point in the path may be described in either of two directions, typically the paths may be ABCA, or ACBA. By the way in which we make the experiment, we determine the direction to be that in which the initial motion is towards more uniform mixture, say ABCA, if B denotes the initial, and C a state of more uniform mixture than B. That is because initially the two gases are *at rest* relatively to one another. As an example, suppose a semicircular smooth tube in a vertical plane with its middle point as base, and in it a heavy particle. The particle, if free to move, and placed at rest at a point above the lowest, will begin by moving downwards. But it will oscillate about the lowest point, and will not move irreversibly to the lowest point. The reason why it begins by moving downwards is because it starts *from rest.* For precisely the same reason the two gases, each *at rest relatively to the other*, begin by moving towards the more uniform mixture. But there is no proof that the motion is irreversible.

21. It is true no man has ever observed them to begin to separate. But to make this evidence of the irreversibility, it would be necessary to continue the experiment for a time at least equal to half the period, if the motion be periodic. And not only that, but also to completely protect the system from all disturbances from without during the whole time. Has this ever been done? And as regards external disturbances, can it be done? If practically it cannot be done, then it may be that in any experiment that can practically be performed, the motion will appear to be irreversible, because the external influences prevent it from being periodic. But then they also prevent the argument from being applicable.

22. If the diameters of the molecules were so small that no collisions occurred, the motion must be periodic. Can it be proved that collisions convert it into an irreversible motion?

23. I think we unconsciously derive the idea of the motion being irreversible from Boltzmann's H Theorem, which is supposed to prove that an irreversible motion of a gas is possible, and that, I think—although the weight of authority against me is immense—rests on "a misuse of the theory of probabilities."

We suppose that at an initial instant the co-ordinates and velocities of the molecules are distributed at haphazard, subject to the conditions (1) that the total kinetic energy is a given constant T, and (2) that Boltzmann's function H has a value greater than its minimum. And we then prove that $\frac{dH}{dt}$ is, under those circumstances, much more likely to be negative than positive. That is true. But the initial values of the variables having been once assumed, their values after any time t are determinate functions of the initial values and of t. The law of probabilities has nothing further to say in the matter, but having fixed the initial values is *functus officio.*

24. The error consists, as I maintain, after the manner that men call heresy, in assuming the law of probabilities to have continuous action, as though an independent haphazard distribution of the variables took place at every instant. If that were the case, it is true that $\frac{dH}{dt}$ would be on an average negative at every instant, and the motion could not be periodic. There are, in fact, at the initial instant a great number, say n, of possible states of the system, and as many possible determinate courses for all subsequent time. By the way in which we make the initial distribution, each of these n states, with its determined course, is as likely to happen as any other. Further, as we are in complete ignorance of the sequence of events in any one of the n courses, it is true that, to our minds subjectively, each state of the system is at every instant as probable as any other. But this ignorance of ours would exist in fact whether the motion be periodic or irreversible. We cannot therefore argue from our ignorance of the courses that the motion is irreversible. For this reason I think the usually accepted proof is illogical.

25. Further, the objection to the H Theorem, first made, I believe, by Loschmidt, that if all the velocities were at any instant reversed, the system would retrace its course, is, to my mind, fatal to any theorem of irreversible motion in a gas whose molecules are such as the kinetic theory assumes, provided that the isolation of the system be complete. Of course, if a fresh haphazard distribution took place at every instant, as the theory requires, the Loschmidt objection would fail altogether, for on reversal of the velocities the system would *not* retrace its course. And any external disturbance,

coming at haphazard, independently of the existing state of the system, effects a new distribution *pro tanto.*

26. I know it is said in defence of the theorem that the reversed motion, though possible, is highly improbable. But if the H theorem be true, Maxwell's law of distribution of the velocities must be assumed to prevail ultimately, or anyway cannot be denied by advocates of the theorem. From which it follows that any course and the reversed course are equally probable. To say that one of the two is the more probable *because it leads to H diminishing* would be a *petitio principii.*

27. If, as I think is the case, the complete protection of two diffusing gases from all external influences continuously for a very long time is impossible, the motion is, as I have said, for that reason irreversible, because the external disturbances are equivalent to a new haphazard distribution. But for that same reason the irreversibility does not necessarily involve increase of entropy, and the whole argument falls to the ground.

28. I have asserted generally that if the molecules of gases are what they are assumed to be in the kinetic theory, no irreversible motion is possible in an isolated system. Very probably it may be necessary to revise our conceptions of a molecule, and Prof. Bryan's work may well be conducive to that end.

THE PRICE OF ANÆSTHESIA

By AUGUSTUS D. WALLER, M.D., F.R.S., LL.D.

The debate that took place a few weeks ago through the columns of *The Times*, between the scientist who finds his public too ignorant to understand him and the public who finds that the scientist talks a learned jargon that is a sign and symptom of his own imperfect knowledge, is one that should not fail to be heeded by any person making bold to say something in the pages of Science Progress. For we are, all of us, in relation to each other's work and thought, very public indeed; the barrier of language is raised not only between scientists and public, but between scientists and scientists, and the public is hardly to be condemned as ignorant if the instructors themselves remain immured from each other, as well as from "the public," in their private apartments of thought and language.

If it be true that nothing new in science is achieved otherwise than by "constantly thinking unto it," it is equally true that "the greatest thing a human soul does in this world is to see something, and *tell* what it saw in a plain way.

I am perhaps rashly challenging an adverse verdict by proclaiming at the outset a standard of excellence that I may hardly hope to reach—that I shall, however, attempt to reach—by telling in a plain way something that I have seen.

Chloroform, the anæsthetic *par excellence*, that has conferred upon mankind the great boon of surgical anæsthesia, is known, or will one day be known, to the vast majority of us by actual personal experience. That is a first reason to enlist our interest. It is one of the most efficient and certain poisons known; its certainty and regularity of action are such that it is systematically used for mercifully getting rid of lost dogs, and an unknown but considerable number of persons annually lose their lives in consequence of chloroform administered for the purpose of producing surgical anæsthesia—"skilfully administered for a necessary surgical operation," to quote words frequently employed by coroners' juries. The number of officially recorded deaths in England registered as due to anæsthetics during the ten-year periods was:

1866 to 1875	146 deaths.
1876 „ 1885	264 „
1886 „ 1895	533 „
1896 „ 1905	1,269 „

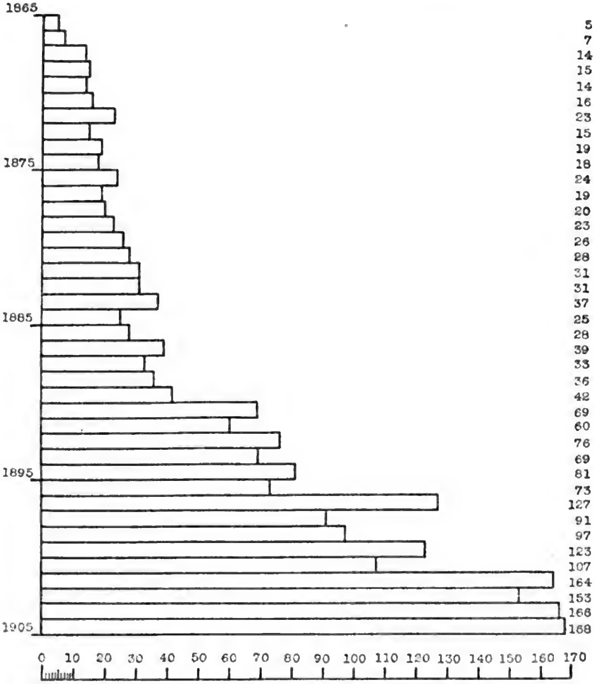


FIG. 1.—Diagram of the annual number of deaths registered in England and Wales as due to anæsthetics in the years 1865—1905.

Now, this is a heavy price to pay for even the great boon of anæsthesia; for it is an unnecessary price—a toll levied in all good faith by reason of a neglect of the most elementary knowledge of the physical and physiological properties of chloroform.[1]

I do not say that such neglect is universal, and that there are not exceptional administrators of experience and natural skill such as to entitle them to be considered "safe," but I do say that the general practice of the overwhelming majority of persons, whether medical or non-medical, who are necessarily called upon to administer chloroform, is dangerous, and must unavoidably kill a certain number of patients and endanger the lives of many more, and produce an incalculable amount of alarm and uncertainty in connection with anæsthesia.

And I shall hope to show in the course of this article, so as to be understood by any educated person, medical or non-medical, that this heavy price is paid for lack of a little elementary science—not science expressed in Græco-Latin neologisms, but science of the A B C character, consisting of simple arithmetical measurements, far less complex and learned-sounding than much of the science that is dispensed by board-school teachers and extension lecturers, but for lack of which even a doctor of medicine is not qualified to administer chloroform.

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[1] I do not think it necessary to enter here into any detailed discussion of the value of these statistics. It has been urged in mitigation of the figures that (1) they include many cases in which death has occurred not *by*, but only *after*, chloroform; and that (2) we should take into account the greatly increased number of operations performed under anæsthesia.

I think that the first error is far outweighed by the opposite error of attributing to other causes deaths that have in reality been due to the anæsthetic. A large proportion of cases of deaths undoubtedly due to chloroform are never published, or are attributed to other causes. How many it is impossible to say. Some years ago, when I went closely into the matter, I found in the case of one hospital, at which two cases had been reported in the year, that nine cases had actually occurred. The late Prof. Julliard, of Geneva, found that twenty cases of death by chloroform had occurred at Geneva, of which three only were reported. And only last January a London coroner, in opening an inquest, stated that "this is the thirty-ninth case of the kind from —— Hospital in the course of six and a half years."

In *The British Medical Journal* of January 25 (p. 202), a case of death during anæsthesia is reported by an anæsthetist under the title "A Fatal Case of Status Lymphaticus"; and the previous pages of the same issue contain an elaborate argument by another anæsthetist to the effect that death during chloroform anæsthesia is so frequently associated with "status lymphaticus" that it may be asked whether death under chloroform ever occurs apart from that condition.

Clearly the price of anæsthesia, as indicated in the returns of the Registrar-General, must be below rather than above the mark. With regard to the probable increased number of operations under anæsthetics during the last half-century, no doubt it has had some influence on the increased number of deaths noted for the later than for the earlier years, but it can hardly account for the figures of the last two decades, in which, while the reported deaths have more than doubled—533 and 1,269—the number of operations can hardly have increased in the same proportion.

Let me premise in the first place that it is totally futile in the case of any poison, whether it be called strychnine or alcohol or aconite or morphia or chloroform, to discuss sources of danger, antidotes, diathesis, idiosyncrasy, etc., etc., without knowing how much strychnine or alcohol or chloroform has been put into the body. It is comparatively easy to learn how much strychnine will kill, rather less easy to know how much alcohol will intoxicate, comparatively difficult to determine how much chloroform will anæsthetise.

Alcohol is more or less measured out, by glass or bottle, and we know that the subject gets more or less drunk after more or less drink; knowing this we are justified in observing that subjects differ, and that qualities of liquor vary; and if necessary we can go on to consider effects of adulterations and effects of idiosyncrasy. But obviously we could do nothing of the sort unless we could measure quantities of poison swallowed.

But in the case of chloroform, which is administered by inhalation through the lungs, the effects of adulteration and the effects of idiosyncrasy have been discussed in the absence of any approach to such a measurement. The patient has as a rule inhaled an unknown quantity of chloroform. As a rule the administrator has not the slightest idea what the quantity has been, and a fatal accident that has in all probability been caused by overdose is put down to idiosyncrasy of patient or impurity of chloroform.

Is it not clear that the first necessary step to take, previous to any possible rational discussion of idiosyncrasies and impurities, is to find means of measuring the quantity of chloroform absorbed, or at any rate of measuring the quantity of chloroform in the air inspired?

My attention was forcibly directed to this question in 1890, in connection with physiological experiments. Whereas in my previous clinical experience I had had occasion to administer chloroform fairly often in the rough-and-ready fashion of the Edinburgh school, without mishap or alarm, in my subsequent laboratory experience I frequently lost animals by overdose of chloroform, and for a time I took to ether instead.

From this I was led to make a long series of experiments on isolated nerve with ether and with chloroform vapours at all kinds of percentages in air. Using the excitability of nerve as my touchstone, I found that 10 per cent. chloroform vapour was immediately and irremediably fatal, while ether vapour at much higher percentage caused complete but only temporary inexcitability. I studied in the same way many other anæsthetic drugs—the chloromethanes and chloroethanes especially, and chloroform itself at percentages from 0·5 to 5 per cent. I came to the conclusion that chloroform is physiologically seven times as powerful as ether, that as a certain and controllable anæsthetic, chloroform is the best of the chloromethanes, and preferable to any of the various chloroethanes that have been recommended from time to time for clinical use, but that the safe administration of chloroform requires the continuous and uniform inhalation of chloroform and air at between 1 and 2 per cent.—or, as I then expressed it for the sake of emphasis, "not below 1 per cent., not above 2 per cent."

In the discussion that took place on the communication of these results at the meeting of the British Medical Association at Montreal[1] (1897) and in the following year at the Society of Anæsthetists, the principal points of opinion elicited were to the effect that it was certainly desirable that chloroform should be administered with plenty of air, but that it was practically very difficult if not impossible to secure the administration of the vapour between any definite limits of percentage.

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[1] Waller: "The Action of Anæsthetics on Nerve; Ether and Chloroform," *Brit. Med. Journ.*, November 20, 1897.

Waller: "On the Dosage of Chloroform," *Brit. Med. Journ.*, April 23, 1898.

Waller: "On the Administration of Chloroform to Man and to the Higher Animals," *Lancet*, November 28, 1903.

Waller: "On the Physical Relation of Chloroform to Blood," *Proceedings of the Royal Society*, Vol. 74, 1904, p. 55.

Waller and Geets: "The Rapid Estimation of Chloroform Vapour," *Brit. Med. Journ.*, June 20, 1903.

Waller: "Chloroform Estimation by Densimetry": "Ether Estimation by Densimetry," *Proceedings Physiological Society*, July 11, 1903.

Waller and Collingwood: "Estimation of Inspired and Expired Chloroform," *Proceedings Physiological Society*, February 25, 1905.

Waller: "A Physiological Contribution to the Problem of Chloroform Anæsthesia," *Brit. Med. Journ.*, December 24, 1904.

Waller: "On the Action of Anæsthetics," Presidential address to the Physiological Section of the British Association, Leicester, 1907.

This opinion was, I think, in the main correct. Snow's inhaler, in which the patient inspired through a bottle containing liquid chloroform, had been found to be not free from danger, the *estimated* percentage was rather high (4 per cent. or 5 per cent.) and the apparatus fell into disuse until recently, when it was revived under a slightly different form by Vernon-Harcourt, and favourably reported on by a committee of the British Medical Association.[1] The percentage of delivery of this modified form is adjusted to be from 0·5 to 2 per cent., but in my opinion the percentage scale with which the instrument is furnished is no real indication of the actual percentage of delivery. The method is the everyday method of the laboratory, where prompt rather than safe anæsthesia is required; but obtained at a price of accidental deaths by overdoses with which every physiologist is familiar.

Paul Bert's method to deliver to the patient chloroform and air at known percentage from a large gasometer proved to be quite impracticable.

Another French apparatus, that of Raphael Dubois, has fallen out of use in France, and has been condemned in this country as being cumbrous and expensive. It is, as I have elsewhere stated,[2] a very safe apparatus indeed, and my opinion has been confirmed during the last three years by the far more extensive experience of Dr. Paul Chapman, of Hereford. I believe, however, that the method is inferior both in certainty and in convenience to that which I shall finally describe.

An apparatus of my own,[3] called the wick-vaporiser, based on the principle of the carburettor of a motor-car, and adjusted to deliver by the evaporation of chloroform from 1, 2, or 3 wicks, 1, 2, or 3 per cent. of chloroform vapour, has rendered good service in the laboratory, has proved satisfactory in a limited number of trials in hospital, but is open to an objection that applies in more or less degree to all other forms of apparatus

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[1] *Brit. Med. Journ.*, July 1903.

[2] "An Examination of Apparatus proposed for the Quantitative Administration of Chloroform," *Lancet*, July 9, 1904.

[3] "The Wick-Vaporiser," *Proceedings of the Physiological Society*, August 19, 1904; *Journal of Physiology*, vol. xxxi.

I have examined: viz. the graduation, however carefully made in the laboratory, is illusory when copied by the instrument-maker, and still more illusory in the hands of an anæsthetist.

The Roth-Dräger apparatus is designed to supply a mixture consisting of a measured volume of oxygen and a measured volume of chloroform vapour from a measured number of drops of liquid chloroform. The apparatus has been used largely in Germany during the last four or five years. I tested it in 1904, and found that the delivery is approximately in accordance with the graduation of the scale. The apparatus is, however, cumbersome and complicated, more so than the Dubois.

But I do not propose to encumber these pages with the detailed description of particular apparatus. All I wish to do is to make good the point that the necessity of measurement has given rise to measuring apparatus in France, in England, and in Germany. All such apparatus applies one or other of two principles—the chloroform mixture being supplied to the patient on the vacuum system—Snow, Vernon-Harcourt; or on the plenum system—Dubois, Junker, Waller, Roth-Dräger. On the vacuum system, the patient inspires air through a vessel containing liquid chloroform by a broad inlet tube and a closely fitting face-piece. On the plenum system the patient inspires from a freely open face-piece in which an excess of chloroform and air of required percentage is maintained by a pump. Obviously the former method is more difficult to apply perfectly than the latter.

The most serious objection to every sort of graduated apparatus is, however, the fact that the graduation, valid in the laboratory to an error of perhaps 10 per cent., is liable to variations of 100 or 200 per cent. in hospital use. The value of any scale of any sort of graduated apparatus used under clinical conditions is less than none, for the graduation is misleading. Variations of temperature, of ventilation, agitation, etc., may at once cause the unit percentage to rise to 2 or 3, or to fall to ½ or less, and the scale becomes completely misleading—1 may mean 2 or 0·5; 2 may mean 4 or 1; 0·5 may mean 1 or 0·25—and any discussion as to what percentages are safe or dangerous is waste of time. Indeed, when one asks by what methods percentages are determined, he must marvel at the facility with which it has become customary for anæsthetists to talk about this or that percentage of chloroform. All the same, this loose talk in terms of percentage is a considerable step in advance of the state of matters a few years ago, when anæsthetists were accustomed to scout the possibility of any sort of measurement, and to judge of the action of chloroform solely by its result upon the patient. Obviously, under such conditions, the only safe anæsthetist was the experienced anæsthetist, the man who had learned to recognise danger as soon as danger became visible. No man can be thus experienced from the outset, some men become thus experienced more rapidly than others, others never become thus experienced. Is it not, therefore, self-evident that in every few thousand administrations there must be cases of serious danger or death, and that in every single administration there must be anxiety or alarm? And may it not be expected of science, which is measurement, that the heavy price of anæsthesia should be reduced? I assert again what I have already asserted repeatedly in medical circles—at Montreal before the British Medical Association, at the Society of Anæsthetists in London in 1898, at Johannesburg to the Physiological Section of the British Association in 1905, in many communications to the *British Medical Journal* and *Lancet*—that the price need not be paid, or, at least, may be greatly reduced, by the application to medical practice of two or three simple lessons of arithmetic learned in the physiological laboratory.

It was estimated by Snow[1] that 18 minims of chloroform in the blood of a patient will produce anæsthesia, and that double the amount is fatal.

Gréhant estimated that the blood of animals killed by chloroform inhalation contained about 50 milligrammes per 100 grammes.[2] This proportion would be about 2½ grammes in the blood of an average person.

Buckmaster and Gardner[3], by a more precise method, arrived at an almost identical result. The amount of chloroform in the blood of an animal killed by inhalation of strong vapour was from 40 to 60 milligrammes per 100 grammes; that in the blood of an animal completely anæsthetised was 20 to 40 milligrammes. And following out the percentage in the course of anæsthesia, they called attention to the fact that at the very outset the percentage commonly reaches a maximum value within the first minute or two, and thus gives rise to "a first danger point" during the induction of anæsthesia.

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[1] Snow, *On Chloroform and other Anæsthetics*, 1858. 18 minims is approximately 1 c.c. of liquid chloroform, or 300 c.c. of chloroform vapour. 1 gramme of liquid chloroform gives approximately 200 c.c. of vapour.

[2] Gréhant et Quinquaud, "Dosage du Chloroforme dans le Sang d'un Animal anesthésié," *Comptes Rendus de l'Académie des Sciences*, xcvii. 1883, p. 753.

[3] Buckmaster and Gardner, "The Estimation of Chloroform in the Blood of Anæsthetised Animals," *Proceedings of the Royal Society*, vol. 79, 1907, p. 309.

As ordinarily administered, it is quite possible that a patient should take into the lungs in one minute 10 litres of air, containing 4 per cent. of chloroform vapour, *i.e.* 400 c.c., of which one-half may be at once absorbed by the pulmonary blood and carried to the heart, *i.e.* 200 c.c. or 1 gramme, or one-half the quantity reputed to be lethal. Merely by a single deep gasp after the breath has been held, it would be quite possible for a patient to take suddenly into his lungs perhaps 100 c.c. of vapour, or half a gramme of liquid chloroform. Is it to be wondered at that a heavy price is paid for the boon of anæsthesia? Is it not, rather, matter for surprise that the price is not heavier than it is?

The principal condition upon which the required state of anæsthesia depends is the mass of chloroform present in the inspired air, or, in other words, on the tension of chloroform vapour in the lungs. And it is important that, as far as possible, the percentage (or tension) of chloroform vapour in the inspired air should be kept as constant as possible by the continuous administration of chloroform at low percentage. The intermittent and irregular administration at high percentage should, as far as possible, be avoided. In comparison with the fulfilment of this principal condition all other considerations are of subordinate importance—the fact that the administration should be commenced at relatively low percentage, and once anæsthesia is induced that it can be maintained at low percentage; the fact that patients differ in their susceptibility to anæsthetics; the fact that more or less profound anæsthesia is required, according to circumstances; and many other detailed facts, to the scientific control of which it is primary that we should know how much chloroform is actually delivered to the inspiration of the patient, or, rather, what is the actual percentage and tension of chloroform vapour in the inspired air.

Some ten years ago I said that the percentage should be between 1 and 2. During the last few years I have elaborated a ready method of estimating that percentage, and have attempted to devise a ready method of delivering chloroform vapour and air between the required limits.

I have at last hit upon a combined method of estimation and of delivery that has proved itself to be an admirable laboratory method, and that will, I believe, prove to be of great service as a hospital method of exact administration.

The arithmetical data upon which the method depends are as follows:

A litre of chloroform vapour weighs .	5·3	grammes
„ air „ „ .	1·3	„
Difference	4·0	„
Or difference per 1 c.c. .	4·0	milligrammes

A litre of chloroform and air at 1 per cent., or 990 c.c. of air + 10 c.c. $CHCl_3$, weighs 1·34 grammes, and every 40 milligrammes of weight in a litre flask or bulb of mixture indicates 1 per cent. of chloroform vapour in the mixture—or in a 250 c.c. bulb each centigramme indicates 1 per cent. This affords a ready means of estimating from time to time the percentage of chloroform vapour in mixtures of chloroform and air, and I have used it extensively as a means of calibration and control of apparatus. But, obviously, it is not a method for use outside the laboratory.

But the next step, by which I sought to obtain for the laboratory a means of estimating from moment to moment, and recording, the fluctuations of percentage taking place in the chloroform mixture delivered to an animal, and of varying the percentage as desired for the experiment, put me in possession of an instrument which at once fulfilled its laboratory purpose and at the same time is obviously capable of being transferred to the operating theatre.

Instead of weighing in air a bulb full of chloroform mixture, I weighed, or rather counterpoised, a bulb full of air in a jar traversed by the chloroform mixture; the bulb, of course, rose and fell as the mixture was made more or less dense by more or less chloroform vapour. The pointer of the balance was then graduated in chloroform percentages by appropriate weights—increments of 40, 80, 120 milligrammes for 1, 2, and 3 per cent. $CHCl_3$ with a litre bulb.[1] A light pen fixed to the beam of the balance and a smoked cylinder served to give a record of the rise and fall of the bulb with rise and fall of chloroform percentage, and incidentally served the useful purpose of damping the oscillations of the beam and pointer. In order to avoid accidental fluctuations of the percentage delivered to the animal, it was advisable to use a vessel of considerable volume containing the mixture on its way to the animal. I used the case of the balance for this purpose. Air was pumped into it through or over the surface of chloroform by the ordinary respiration pump or by a bellows, and went on by a second tube to the tracheal cannula or mask. The large capacity of the balance case—in this case 30 litres—proved to be suitable for the induction of anæsthesia and for its safe gradual modification. The chloroform percentage rose from zero to 2 per cent. in about two minutes; the lag of voluntary diminution and increase was about ten seconds; the pointer could at will be kept perfectly steady at any desired percentage. Finally, I may remark that for all ordinary purposes of the laboratory a comparatively coarse balance is best adapted. In the apparatus now in daily use the graduation is from 1 to 3 per cent., which gives records of 6, 12, and 18 mm. amplitude.

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[1] I have not talked about temperature and pressure corrections, which should be taken into account when required, and ignored when not required. For

Judging by the comments of visitors to the University of London, acquainted with the various haphazard methods in use for producing and maintaining anæsthesia of the human subject, and witnessing for the first time the ordinary procedure followed in the physiological laboratory for the producing and maintaining of anæsthesia of animals, the usual thought aroused seems to be one of regret that the human subject cannot be anæsthetised with similar uniformity and safety.

My own feeling is one of intense surprise, that the clear practical experience of the laboratory should be of so little use to the medical profession, and that year by year the death-roll of chloroform anæsthesia should continue undiminished.

Occasional attempts have indeed been made in France, in Germany and in England, to bring graduated apparatus into use, and have met with a certain amount of success in the

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ordinary temperatures (18° C.) and pressure (760 mm. Hg) a bulb of 1054 c.c. would be required for these increments. Or if, as was the case of the particular balance now in my hands, the bulb had a capacity of 870 c.c., the counterpoising weights for 1, 2, 3 per cent., should be taken as 33, 66, and 99 milligrammes.

hands of a few anæsthetists. But for one reason or another, graduated apparatus has not met with general favour; instruments have been too dear, or too troublesome, or have failed to fulfil the promise of their inventors and advertisers. Each inventor, whether French or English or German, has had his instrument patented; and the consequence has been that each instrument has been advertised as perfect, whereas as a matter of fact no instrument can be perfect—every instrument requires to be used intelligently.

I think it may be useful to describe the ordinary daily practice of this laboratory towards animals, and to indicate as briefly as possible how I should propose that a similar procedure should be applied to hospital anæsthesia. And I shall at once premise, in reply to the inevitable objection that the method is too troublesome for hospital use, (1) that it is not too troublesome for daily use in the laboratory for animals, (2) that several thousand animals have been anæsthetised in this laboratory during the last five years, without the accidental loss of a single animal, and (3) that, even admitting that the procedure is more troublesome than the ordinary practice, it is not unreasonable to expect as much trouble to be bestowed upon the safe anæsthesia of a patient in a hospital as is bestowed upon an animal in a laboratory. In point of fact, the trouble of application would be smaller in the case of man than it is in that of an animal.

The procedure in this laboratory as regards animals is as follows:

First step.—The animal is placed in a closed glass chamber (a large bell-jar, or a small cupboard with plate-glass front), into which chloroform-and-air of desired percentage is pumped. The latter is provided by pumping air by a small electric motor through an ordinary wide-mouthed bottle containing liquid chloroform, into a large-mixing chamber (capacity = about 30 litres), containing the chloroform balance and provided with an inlet from the chloroform bottle and an outlet to the animal chamber. The flow of air is rendered uniform and of suitable volume per minute by means of an elastic reservoir and a perforated stop on the course of the supply tube. The percentage of the mixture administered is watched on the pointer scale (and if desired recorded by a light pen). It is regulated by varying the depth of a tube in the chloroform bottle and by admitting more air to the mixing chamber. In general, anæsthesia is induced by chloroform and air at 2 per cent., and the animal is kept under anæsthesia at 1 per cent. until required.

Second step.—The anæsthetised animal is removed from the bell-jar or cupboard, for the operation of tracheotomy. The outlet tube of the mixing chamber is attached to the tracheal tube, and anæsthesia is maintained by a mixture at between 1 and 2 per cent., as shown by the index of the chloroform balance. The chloroform-and-air is taken by the animal by its ordinary respiration, or supplied to the animal by the action of the pump (in which case the elastic bag and perforated stop are removed from the supply tube). In either case the anæsthetic vapour is under slight positive pressure—*i.e.* it is delivered on the plenum system.

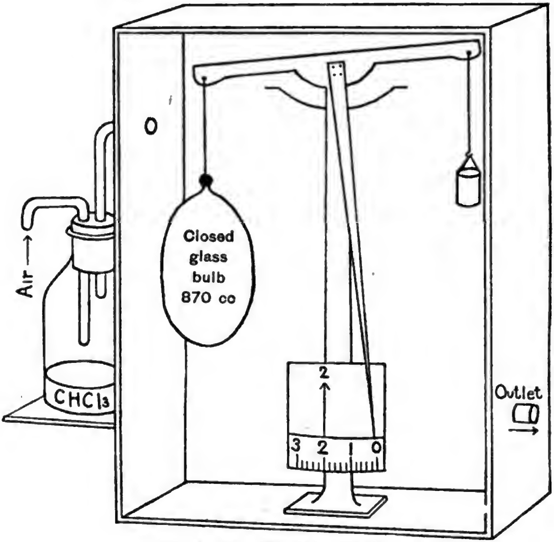

FIG. 2.—The Chloroform Balance.

The *procedure in hospital* is (or would be) simplified by the fact that the first step necessary in the case of animals, viz. anæsthesia in a confined space, is not necessary for the human subject. Obviously, also, tracheotomy is omitted; all that is required for the human subject is an open mask or face-piece at the end of the delivery tube. For since the delivery of chloroform to the patient is on the plenum principle, and such pressure as exists in the mixing chamber and delivery tube is positive, length of tube is immaterial, and does not place any extra work upon inspiration by the patient. All the apparatus required by the anæsthetist at the operating-table consists of the tube itself, and the face-piece or other terminal contrivance; the pump, the chloroform bottle, the mixing chamber, and the chloroform balance are at a distance from the operating-table, out of the way, but not out of sight. The size of the mixing chamber (30 litres) ensures the continuous and uniform supply to the patient of chloroform (or ether) vapour at known and visible dilution. The indication of percentage is easily verified, and is visible to all persons present. The concentration, which, by reason of cooling of the chloroform, automatically remains below 3 per cent., can be varied at will with sufficient rapidity, as shown by the indicator, and it cannot be suddenly augmented to a dangerous amount. The attention of the anæsthetist is free to be wholly bestowed upon the state of the patient, in accordance with which the strength of vapour is raised or lowered, and *seen* to be raised or lowered. (At the cost of a very trifling additional trouble, a permanent record can be taken of the strength of vapour employed during the whole time of its administration.)

The apparatus in its laboratory form is not very portable. And although, no doubt, it may be practicable to render it more portable, I prefer at present to keep to the dimensions with which I am familiar, and to advise its use chiefly as a hospital fixture, set up in the operating theatre and in the room or rooms in which patients are prepared for operation. I am convinced that an installation of apparatus of this character would go far to remove the possibility of prolonged series of fatalities such as that mentioned in the footnote to p. 612, and to allay an incalculable amount of anxiety in the minds of all those who know. And as regards the general public, who at present do not know, I am convinced that if the serious misfortune of an unreasoning dread of anæsthetics is to be avoided, the danger of anæsthesia must be reduced to whatever may be its unavoidable minimum, by applying in the hospital the clear teaching of the laboratory.

A direct indicator of the percentage of chloroform in the air delivered to the inspiration of a patient is, in my opinion, a valuable safeguard. It is not difficult to secure; it is legible at a glance. I do not say that its use would abolish all danger, but I do assert that the common knowledge of the physiological arithmetic of chloroform would go far to diminish the excessive price of anæsthesia.

RECENT RESEARCHES ON CHLOROFORM ANÆSTHESIA

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ANY one who at the present time reflects upon the advances which have taken place in medical practice within the last twenty-five years will easily recognise that the introduction of antiseptic and aseptic methods—for which all mankind is under a lasting debt to Lord Lister—has largely increased the frequency of surgical operations. The frequency with which general anæsthetics are employed has consequently also augmented to an equal or even greater extent, and it may be admitted that the safe administration of such a drug as chloroform is to a large extent dependent upon the skill of the individual anæsthetist. However, deaths may, and do, occur during anæsthesia. Life may be lost before an operation has been commenced, and the cause or causes of such an accident has been the subject of much useless speculation, and also of some valuable experimental work on the physiology of anæsthesia. The whole science and art of medicine advances sometimes at a slow, sometimes at a quicker rate, but any given degree of progress is almost entirely regulated by those additions to knowledge which are founded upon exact experiments carried out in laboratories.

During the past few years the subject of anæsthesia by chloroform has been under the consideration of a special committee appointed by the British Medical Association.[1] The experimental work thus initiated has proved of much service, especially in indicating the limit-value of the chloroform vapour which can be safely inhaled. The introduction of an inhaler by Vernon Harcourt for the administration of chloroform with safety is also the direct outcome of this work. The simplest and quickest way to determine the percentage of chloroform vapour in air is by a method suggested by Waller,[2] which depends upon the proportional increase in weight which known volumes of air and chloroform exhibit, compared with the same volume of air. The purpose of this paper, however, is to draw attention to recent work on chloroform anæsthesia which has been carried out in this country and in France. The activity of observers in Germany has not been directed to this particular inquiry.

Besides chloroform, some hundreds of substances have been shown to possess in different degrees well-marked anæsthetic and narcotic properties. All forms of life, the simplest and the most complicated, unicellular and multicellular organisms, can be shown to exhibit very similar phenomena in response to minute, moderate, and toxic doses of those drugs which are grouped as anæsthetics; and it is probable some single fundamental type of interaction which takes place between the anæsthetic and the protoplasm or bioplasm of cells, will be found to take place, and that upon this fact a rational explanation of the anæsthetic process will be given. The condition finally established by increasing any given anæsthetic is one of profound intoxication, and a state of narcosis is induced in the higher animals, owing to the successive interference with the excitability of the cortex of the brain, of the grey matter of the spinal cord, and of the grey matter of the spinal bulb or medulla oblongata. These parts of the central nervous system become inactive, and a progressive paralysis of the nerve cells becomes established, in which the sensory and receptive apparatus is probably impaired before the motor. It is beyond dispute, as any one must admit who is familiar with the subject, that the anæsthetic state is a condition where the tissue elements, or cells of the body, are poisoned in different degrees, and the cells of the central nervous system in higher animals exhibit a peculiar elective or selective power in picking up such a drug as chloroform, compared with other portions of the excitable tissues or neuro-muscular apparatus of the body. No matter by what particular hypothesis this selective power is explained, it is equally certain that chloroform does not actually accumulate in the tissues, or remain permanently held by protoplasm, for a restitution of the normal functions of the whole body is always to be seen, provided that the interference with function has not been of too long a duration.

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[1] *British Med. Journal*, July 12, 1902, July 18, 1903, July 23, 1904, July 22, 1905, July 14, 1906.

[2] Waller, *Proc. Physiological Soc.* 1903.

As an explanation of the anæsthetic state some observers on insufficient grounds have attributed this to a local anæmia of the cerebral cortex. But it is known that this view is not in accord with experimental evidence, for the opposite occurs in the early stages of chloroform narcosis; and as Roy and Sherrington and also Hürthle have demonstrated, the blood-flow through the brain is actually increased. In profound anæsthesia, the bulbar centres—those complex nerve-cell aggregations which physiologists speak of as the vaso-motor centres, which control the bore of the smallest arteries, so that these are in no sense inert tubes of constant diameter, the respiratory centres controlling the muscular movements of the thorax, and the cardiac nerve-centres, which govern the liberation of energy by the heart muscle—become paralysed. Frequently these centres are finally poisoned in the order in which they have just been mentioned, and then, owing to a vaso-motor paralysis, which is particularly a feature of chloroform poisoning, such a quantity of blood may accumulate in the dilated blood-vessels that a true cerebral anæmia may occur. Here it may be mentioned that experiments upon animals have yielded incontestable evidence that among mammals the vaso-motor nervous mechanism is more perfectly developed in a physiological sense in man than in the apes, in the apes than in the carnivora, in these more than in rodents. As Leonard Hill[1] has shown, the explanation of this perfected mechanism in man is related to his erect posture, and the circulation of blood through the brain is maintained at a normal value, whether an animal is placed in a horizontal position or in the feet-down or head-down position.

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[1] *Journal of Physiology*, vol. xviii. 1895.

From two volumes published last year by a well-known anæsthetist[1] on the chloroform problem, a few remarks may be abstracted, in order to show how the phenomena witnessed in chloroform anæsthesia may lead a skilled clinical observer to views for which at present there is no sufficient experimental evidence, though it is impossible for any one to deny that the deprivation of oxygen may play a very important part in throwing the cells of the neuro-muscular apparatus out of action. The author considers that "chloroform and ether are typical examples of a group of agents which possess the power of abstracting oxygen (from the blood) without otherwise injuring the blood."[2] Again, "all narcotic agents are oxidisable, and cause all their results (direct and indirect) by abstracting oxygen from the blood."[3] "They do not act directly upon the cerebral centres, but indirectly through the intermediation of the -oxy factor, which it would appear is the only known cause of the suspension of their functions."[4] Further, he states that "it is impossible for chloroform to remain in the blood without becoming oxidised; but if there be an excess in the circulation, *i.e.* such an amount as will require more for its oxidation than can be supplied by blood, what influence does the rest exert?"[5] The purpose of this article is not to criticise the views held by any one; but the ideas put forward in this way, supported as they are by no sufficient evidence, are in absolute contradiction to a knowledge which has been most slowly built up by experimental methods. All the evidence acquired by experiments to determine this particular fact, whether any oxidation processes whatever are possible within the blood-stream, has uniformly shown that no measurable consumption of oxygen under any circumstances, even by a substance so easily oxidisable as pyrogallic acid, can be detected with certainty while the blood is within the vessels. It is a cardinal fact, and one accepted by every physiologist, that the consumption occurs within the tissue cells of the body, and that this is dependent entirely, not upon the supply of oxygen, but upon the requirements of the entire organism. The evidence for this is to be found in any physiological text-book. For example, Schmiedeberg found that such easily oxidisable substances as benzyl alcohol or salicylic aldehyde undergo no change within the blood-stream; but that the substances are easily oxidised to benzoic acid and salicylic acid when the blood-flow passes among the cells of the kidney.

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[1] *The $CHCl_3$-problem*, by Richard Gill. 2 vols. 1906.

[2] Vol. ii. p. 275.

[3] Vol. ii. p. 278.

[4] Vol. ii. p. 279.

[5] Vol. ii. p. 267.

The explanation which is advanced—that anæsthesia is due to the abstraction of oxygen by chloroform—rests on no certain basis, for it is quite easy to anæsthetise a frog when all its blood is replaced by ·65 per cent. sodium chloride. Moreover, all animals, including man, who live at varying altitudes from the sea-level to 10,000 ft., are luxuriously supplied with oxygen, so that the amount available far exceeds the need. As will be shown subsequently, the actual amount of chloroform in the blood during anæsthesia is known, and assuming, which is not the case, that it is easily oxidised, the amount of oxygen which might be abstracted in this way would not produce any symptoms at all, except in so far as the oxidation products could exert an effect, and still less possible would it be for a state of anæsthesia to be established by so small a diminution in the oxygen-content of the blood. The destiny of the chloroform in the blood is to be exhaled; and if any amount of it is oxidised this takes place, not in the blood, but in the tissues of the body. Kast[1] and Zeller,[2] also W. H. Thompson,[3] have found an excess of chlorides in the urine after chloroform narcosis; while some observers—Wagener,[4] Thiem and Fischer[5]—state that chloroform as such can be recognised in the urine. An excess of chlorides is not conclusive evidence that the drug is oxidised, for these are increased, but not to the same extent, after anæsthesia by ether.

Experimental evidence that chloroform may be decomposed within the organism has been furnished by Desgrez and Nicloux,[6] who found small quantities of a combustible gas which might be hydrogen methane or carbonic oxide in normal blood. 1000 cc. of this yielded 1·2 cc. of a gas which was apparently carbonic oxide. In the same quantity of blood from animals deeply chloroformed larger amounts were found—in one case 6·9 cc. of carbonic oxide. This increased amount was believed to arise from a decomposition of chloroform. These observations have neither been confirmed nor refuted, but in any case the amount of the drug which was decomposed would be small.

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[1] *Zeitschr. f. physiolog. Chemie*, xi. 1887, and *Jahresber. f. Tierchemie*, xviii. 1888.

[2] *Zeitschrift f. physiolog. Chemie*, viii. 1883.

[3] *Proc. of Physiological Soc.*, January 21, 1905.

[4] *Jahresbericht f. Tierchemie*, xxx. 1900.

[5] *Chem. Zentralblatt*, i. 1890.

[6] *Arch. de Physiologie*, No. 2, 1898.

The most varied types of living animal and vegetable cells respond in an identical manner to the action of chloroform, a drug which is seven to eight times as toxic as ether (Waller). Exceedingly minute doses stimulate living protoplasm; thus, the time of inflorescence of the lilac or azalea is quickened by chloroform vapour.[1] With progressively increasing amounts of the drug, the energy discharges of any organism decrease, and finally disappear with a lethal amount. Both individual cells and organisms differ in the degree of their reaction to anæsthetics; but with a sufficient concentration of the drug, the final result is death. Experiments have shown that dogs and other animals are effectually killed by amounts of chloroform which are incapable of producing anæsthesia—in other words, the metabolic or nutritional processes of the body are profoundly affected, the temperature falls, and death occurs. This phenomenon was clearly described by Paul Bert[2] in 1883, and has been more recently studied by B. J. Collingwood.[3] The following table is constructed from experiments carried out on dogs by Paul Bert:

Percentage of chloroform vapour in air.	Results.	Hours from commencement of administration till death.
·8	No anæsthesia	9–10
1·2	Diminished sensibility	6–7
1·6	Anæsthesia slowly induced	4
2·	Anæsthesia in a few minutes	2–3
2·4	" " "	1·7
3·	" " "	·66
4·	" " "	·5
6·	" " "	·005

It will be seen that the toxic action of chloroform profoundly checks the nutritional or metabolic phenomena of the body; when a low percentage is inhaled an enormous quantity of chloroform can pass into and out of the body without producing any obvious effect except a fall in temperature. In this its action closely resembles alcohol, which has been shown by Tarchanoff to impede growth and check the development of the excitable sensori-motor regions of the cortex of the brain. Chloroform also appears to exert a marked influence on the growth of animals. Experiments have been carried out for a period of five months on kittens from the same litter and of equal vigour, which show that there is a retardation of growth, estimated by weighing, in young animals which were anæsthetised up to the point at which the corneal reflex just disappeared, twice a day. Animals, however, like plants, exhibit increased metabolic activity subsequent to this treatment, and their rate of growth more than compensates for the retardation.[1]

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[1] E. Lemoine, *Jour. of Royal Hort. Soc.* October 1903, and Leblanc, *Soc. Cent. d'Hort. de Nancy*, 1906.

[2] *Comptes rendus de l'Acad. d. Sc.*, t. xcvi. p. 1831, 1883.

[3] Science Progress, vol. i. p. 12.

The Relations which may exist between Chloroform and Blood

It has already been stated that the condition of anæsthesia can be induced in isolated cells or in organisms which possess neither a blood system nor a nervous system. The condition can be established in any living thing, no matter how low or how high may be its organisation. How the anæsthetic state is actually produced is at present unknown, though the theory advocated by Hans Meyer[2] and Overton[3] is generally accepted as affording some sort of explanation. These observers, independently and almost simultaneously, ascribed the action of such an anæsthetic as chloroform to the fact that certain cell-constituents, such as lecithin or cholesterin, were capable of physically taking up or absorbing the anæsthetic. When this has occurred the activities of the cell are interfered with, especially in the sense that its response to excitation is diminished. The greater sensitiveness of the central nervous system, compared with other organs of the body, such as the muscles, is considered to be explained by this hypothesis, since the former is peculiarly rich in bodies, or lipoids, which are soluble in chloroform, or the same idea may be expressed by regarding lipoids as cell-constituents which pick up anæsthetics which are soluble in these. The basis for the theory which has just been indicated rests largely upon physical experiments as to the relative solubility of anæsthetic substances in water and in olive oil. It is true that many anæsthetics, chloroform among them, are soluble in all proportions in oil, while water takes up only ·72 per cent.; but a convincing explanation of what occurs in anæsthesia is not likely to be gained by studies of this nature, no matter how accurately they are carried out; and, moreover, they will not afford an explanation of the action of such narcotics as morphia or conia. For these Overton, to whom we owe the introduction of the term "lipoid," suggests the existence of combinations between the drug and cell-protoplasm, a view which Benjamin Moore and H. E. Roaf have particularly put forward as a possible explanation for the action of all anæsthetic substances. Some of these, such as chloroform, may form easily assimilable and dissociable compounds with the living protoplasm; others, such as morphia, may form more stable compounds, and will therefore probably be more specific in their action.

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[1] Shapiro, *Proc. Physiolog. Soc.* December 10, 1905.

[2] *Archiv f. exp. Pathol. u. Pharmakol.* xlii. 1899, and xlvi. 1901.

[3] *Studien über Narkose*, Jena, 1901.

The attention of Benjamin Moore and H. E. Roaf was first attracted to the subject of anæsthesia by witnessing some experiments performed by C. S. Sherrington and S. C. M. Sowton. If a mammal be killed and the heart removed, this organ can be shown to beat regularly for more than four days if it is supplied with a weak, watery solution of certain inorganic salts, provided that the liquid is saturated with oxygen gas. The heart, therefore, will exhibit a prolonged period of activity outside the body when there is no blood supplied to the organ. This demonstration we owe to F. S. Locke.[1] A concentration of chloroform, added to the liquid which feeds the heart, of 1 in 100,000, produces a constant effect; the vigour of each individual heart-beat is diminished. This effect rapidly appears, and persists for just as long as chloroform of this low but adequate concentration is bathing the interior of the heart. When the solution containing chloroform is replaced with Locke's fluid, the effect on the heart's beat disappears and the contractions regain their normal vigour, to again sink when the weak chloroform solution is substituted. From this experiment, to quote Moore and Roaf, it was clear that chloroform exerted no cumulative action on the living protoplasm of muscle; that is to say, the effect on the cardiac beat was the reduction in vigour to a certain extent and no more. No matter how prolonged was the passage of the chloroform solution, the effect rapidly disappeared when the anæsthetic was removed. Secondly, the effect upon the living cells of the heart muscle depended solely upon the concentration (solution tension or osmotic pressure) of the chloroform in the cell for the time being; and, lastly, the effect at any moment was not at all due to the total amount of chloroform which had been supplied to the heart up to that particular time. Experiments of this nature suggested the view that the effect might be due to some unstable association or combination between the anæsthetic and the cell protoplasm of muscle, and that this existed for only so long as the pressure of the anæsthetic was maintained. Diminish this pressure to zero and complete recovery takes place, the association ceasing to exist; re-establish the pressure and the effect of the anæsthetic once more is witnessed. In the opinion of the writer no other view than this is possible. The condition of chloroform anæsthesia in man can be most satisfactorily comprehended by considering that from the commencement of the inhalation of an air-and-chloroform mixture the pressure of the anæsthetic augments in the blood, and it is this pressure which first of all forces the drug into the lymph and then into the cells of the body, some of these being more permeable and therefore more susceptible than others; the degree of anæsthetisation of the cells being due not so much to the absolute quantity of chloroform supplied, as to the maintenance of a definite pressure of the anæsthetic in the blood. From a large number of experiments which the writer has witnessed, it is clear that no definite fixed relation exists between the proportion of chloroform in the blood and the effect of the drug, for this is determined not by the absolute amount which is held, but by the actual quantity which passes into the cells of the central nervous system, so that the control of these over the liberation of energy by the organism is reduced to a minimum.

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[1] *Zentralbl. f. Physiol.* December 30, 1905.

Since in the higher animals arterial blood is the vehicle by which chloroform is taken up from the surrounding medium and a certain solution pressure of the drug must be attained before anæsthesia occurs, the relations which may exist between blood and chloroform have been the subject of much investigation. The proteins of the blood, both those in the plasma and the red corpuscles, particularly hæmoglobin, have been proved to form definite unstable compounds or physical aggregations with chloroform; and the position taken by the anæsthetic in hæmoglobin is not that of the respiratory oxygen, for the oxygen-carrying power of this protein is in no way impaired or interfered with by the presence of chloroform, though it is quite certain that during narcosis with chloroform arterial blood becomes progressively richer in reduced hæmoglobin. Evidence for the above statements was first given by Benjamin Moore and Roaf,[1] though numerous other observers, such as Pohl, Waller, Wells, and Vernon Harcourt, among others, had recognised with what tenacity chloroform is held by the blood after anæsthetisation, and how difficult it was to recover the drug; so that while the gases of the blood can be evacuated, only ·014 gramme out of ·108 gramme of chloroform in the blood can, as Waller demonstrated, be recovered.[2]

The effect of adding chloroform to blood *in vitro* was described by Preyer in 1871.[3] Formánek[4] more minutely investigated this subject, and proved that when a solution of hæmoglobin was treated with chloroform and kept at a temperature of 50°–53°C. for some time, the protein was so completely precipitated that the filtrate was free from hæmoglobin. Edie's experiments showed that precipitation occurred when the hæmoglobin solution contained from 1·5–7·5 per cent. of chloroform.[5] Even when the amount of hæmoglobin in solution varied and the percentages of chloroform added also varied, the percentage of the anæsthetic in the precipitate to the amount of hæmoglobin which was not precipitated remained constant, from which it may be inferred that the precipitate formed is of the nature of a definite chemical compound or, possibly, a definite physical aggregation.

Experiments *in vitro* have also shown that when a solution of hæmoglobin is taken, and 1 per cent. of liquid chloroform added, and the mixture shaken thoroughly, all the chloroform dissolves; no precipitate forms on standing either at the room or the body temperature. It must, of course, be remembered that experiments of this nature do not in any way imitate the conditions which occur when the vapour of chloroform is inhaled, and under no conceivable circumstances would anything like the amount of 1 per cent. of chloroform ever be found in the blood at the lethal stage of anæsthesia. In 1905 Friedrich Krüger again investigated this point.[1] He states that the precipitate described above is insoluble in water or neutral salt solutions, but is soluble in weak acids or alkalis; and from both of these the precipitate, as might have been expected, is again thrown down on neutralisation. The main interest of Krüger's work, however, lies in the fact that he has described and figured a special absorption spectrum for solutions of this precipitate; and should this observation be confirmed, it would undoubtedly greatly strengthen the views which are held by Moore and Roaf. Just as Edie has observed, so Krüger found that the chloroform-hæmoglobin precipitate was soluble in alkali; but whereas the former observer states that in solution in sodium carbonate yields the spectrum of alkaline hæmatin, Krüger describes the spectrum as one showing two bands, *α* and *β*, which occupy a position very similar to the well-known two-banded spectrum of oxy-hæmoglobin. The spectra are, however, dissimilar.

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[1] *Proc. Royal Soc.*, vol. lxxiii. May 1904, and vol. lxxvii. 1905.

[2] Waller, *Proc. Royal Soc.*, vol. lxxiv. June 9, 1904.

[3] *Die Blutkrystalle*, p. 104: Jena, 1871.

[4] *Zeitschrift f. physiolog. Chemie*, vol. xxxi. 1900.

[5] Reports of Thompson Yates and Johnston Laboratories, Liverpool, vol. vi. 1905.

The difference between these and the effect of reducing agents can be seen from the following:

Spectrum.	**Band *α***	**Band *β*.**	**Effect of dilution with water.**	**Effect of reducing agents.**
Hb + $CHCl_3$ Two bands *α* and *β*	Narrow	Broad intense	Disappear together or *α* before *β*	Reduced hæmoglobin and hæmochromogen
Hb + O Two bands *α* and *β*	Narrow intense	Broad	*β* disappears before *α*	Reduced hæmoglobin

Krüger considers that the effect of reducing agents justifies the conclusion that the chloroform-hæmoglobin precipitate consists of a mixture of hæmatin and hæmoglobin or methæmoglobin. Further, that the relation of chloroform to the blood-colouring matter is not that of an indifferent agent, which simply renders hæmoglobin insoluble, but that this substance is actually chemically changed, though he has not apparently considered the possibility that there might be a linkage between the drug and this protein. Formánek had already described the spectrum seen by Krüger as that of oxy-hæmoglobin, and for the present judgment may be suspended as to the exact spectroscopic characters of this body, especially as Krüger questions the accuracy of many of the existing charts of the spectra of the blood.

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[1] *Hofmeister's Beiträge*, iii. p. 67, 1903.

The facts upon which Moore and Roaf rely as proofs that a true compound or aggregation can, and actually does, take place between chloroform and cell-proteins have been elicited by several different methods which were employed for determining the maximum solubility of chloroform in water, salt solution (·75 per cent.), serum, hæmoglobin solutions, and in blood. The estimated maximum solubility at 13° C. by weight proved that chloroform has a much higher solubility in serum or hæmoglobin solutions than in saline or in water. For example, it was found that the following figures might be taken to represent the maximum solubilities:

	Per cent.
Water	·95
Saline (·75 per cent.)	·83
Serum	5·08–4
Hæmoglobin solutions or blood	6

Determinations of the vapour pressure of chloroform in water, serum, and hæmoglobin solutions were also made with a specially constructed differential densimeter.

It is well known that of the three gases which exist in blood the amounts of oxygen and carbon-dioxide taken up are not proportional to the pressure exerted by these gases; in other words, their absorption does not follow the Dalton-Henry law. The question whether chloroform is or is not taken up by blood according to this law has never been experimentally tested. A given mixture of air and chloroform possesses a definite chloroform vapour pressure in the mixture. If such a mixture is inhaled, the vapour pressure of chloroform in air at the anæsthetising value is found to be about 8–10 mm. of mercury, which was the value observed by Paul Bert. The evidence given by B. Moore and Roaf, who have measured the vapour pressures of chloroform in water, serum, and hæmoglobin solutions of equal strength to that which exists in blood, indicates that the curves of pressures and concentrations in the case of serum and hæmoglobin are such that it is clear chloroform cannot be absorbed according to the Dalton-Henry law, but that the drug is actually associated with the blood-proteins at certain vapour pressures, a fact which is not easy to determine except at high pressures. Conversely, the absorption of chloroform by saline does, as might be expected, follow the law of absorption for varying pressures, and when the results are plotted out the curve is a straight line. At a temperature of 40° C., and at the anæsthetising value of 8–10 mm. of mercury, the coefficient of distribution between vapour-space and solvent for hæmoglobin is about 7·1, and at a room temperature of about 15° C. this would be 18.

Additional experiments performed by Moore and Roaf render the views of Overton and Hans Meyer, which have obtained such wide credence, somewhat improbable. At equal concentration of chloroform in water and saline the vapour pressure of the drug always exceeds what is found for hæmoglobin or the protoplasmic cells of the heart, brain, or muscle; in other words, the association of the anæsthetic with proteins lowers the vapour pressure, just as the tension of oxygen in the blood is low, owing to its association with hæmoglobin. The theory which ascribes the action of general anæsthetics to a relationship which becomes established between the lipoids (substances of the cell soluble in ether, such as lecithin and cholesterin) does not conform with the experimental fact that ethereal emulsions of the brain, which organ is considered to be so specifically affected by chloroform, behave exactly like water or saline solutions; in other words, obey the Dalton-Henry law as far as chloroform vapour is concerned, while emulsions of the entire brain, cells and lipoids show that this law is no longer followed, but that there is undoubted association of the anæsthetic at high vapour pressures. Further, comparative determinations of vapour pressure and concentration of chloroform vapour leave no doubt but that it is the proteid constituent, and not the lipoid material, which is responsible for the actual physical aggregation or chemical combination which takes place. Far from the anæsthetic state being 'due to an affinity of the lipoids of the cells for an anæsthetic, the existence of such substances in bulk, as is the case for individuals who possess a large quantity of fat, actually imprisons a quantity of the anæsthetic which is given, so that it is no longer available for poisoning the cells of the organism, which is essential if anæsthesia is to occur, for it is well known to anæsthetists that the greater the bulk of fat in a patient the greater will be the absolute amount of chloroform required. It is known that the actual bulk of an individual is the gross weight minus the stored fat; the presence of this reserve material in anæsthetisation actually subtracts and renders useless some of the chloroform which is administered.

What may be the actual chemical and physical effect of anæsthetics on protoplasm generally is a difficult problem, and one method which may be applied to its solution depends upon a study of the differences of potential which may follow the subjection of living nerves to anæsthetic vapour of known strength. N. H. Alcock[1] has extended the work of Waller,[2] and, in particular, has investigated the effect of chloroform and ether upon the current of injury which occurs in excised living nerves. A difference of potential existing between the longitudinal and transverse section of the nerve slowly declines under normal conditions, but the difference suddenly drops temporarily or permanently according as the vapour is weak or strong (12 per cent. or more). By subjecting certain regions of a nerve to chloroform vapour, it was noticed that an increase of the injury current, roughly proportional to the strength of the anæsthetic, occurred only when the vapour reached the cross section; applied to the longitudinal surface it caused a decrease.

The resistance of nerve is not affected by chloroform, and therefore no formation of ions at the expense of the electrolytes in the nerve takes place, but the normal polarisation of the nerve is markedly diminished.

A very significant fact is noted with regard to the conductivity of nerve before and after chloroform and ether. While the polarisation of the nerve was markedly altered (as Waller had found) there was no change in the electrical conductivity proper. If this is substantiated it would show that no fresh ion formation took place, and that no splitting up of ion-proteid occurred. In a second paper,[3] Alcock showed that while there might or might not be a combination of chloroform with the proteid of the frog's skin, the electrical effects could only be accounted for by supposing the existence in the tissues of either membranes or surfaces of separation, so arranged that normally certain ions could traverse the membranes and others could not, while after chloroform these membranes or surfaces were destroyed. A simple combination of proteids, as in Moore and Roaf's theory, or with lipoids, according to Meyer and Overton, with chloroform would therefore be insufficient to account for the phenomenon of anæsthesia.

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[1] *Proc. Royal Soc.* vol. lxxi. p. 264, vol. lxxiii. p. 166, vol. lxxvii. p. 267.

[2] *Proc. Physiological Soc.* November 13, 1897.

[3] *Proc. Royal Soc.*, B., vol. lxxviii. p. 259.

The Anæsthetic and Lethal Quantities of Chloroform in the Blood.

In 1860 Lallemand, Perrin, and Duroy stated that 100 grammes of blood contained 1 cc. of chloroform vapour. This was the lethal amount. In 1883, from the results of seven experiments, Gréhant and Quinquaud concluded that 50 milligrammes of chloroform in 100 grammes of blood was the anæsthetic quantity, which was only slightly less than the amount present at the lethal stage. It will be seen subsequently how very exact were both these determinations. Pohl's work in 1890 introduced a new method for the determination of chloroform in blood, and his chief conclusions were that the quantities of chloroform in the arterial blood of dogs during anæsthesia might vary. In some cases 100 grammes of blood contained ·05 gramme, in others only ·029 or ·018 of chloroform. The average lethal amount was ·035 gramme. Pohl also recognised that the lethal and anæsthetic amounts closely approximate one to the other. For about sixteen years no further researches were undertaken in connection with this question, but it was from time to time made abundantly evident that an accurate determination of the chloroform-content of blood was one of difficulty, owing to the tenacity with which the drug was held by the blood, so that it could only in part be recovered from that liquid or from the tissues of the body. During 1906 several French observers, and Buckmaster and Gardner in this country, have renewed this inquiry, and though the methods which have been employed in France and England are quite dissimilar, there is a fair uniformity in the results. The determinations of chloroform in the blood, made by M. Nicloux, St. Martin, J. Mansion, and Tissot, depend upon the titration of the chloroform as chlorides, which are obtained from the blood by distillation with alcohol, rendered acid with tartaric acid, and subsequent saponification with alcoholic soda or potash. The end point of the reaction is a colour one, yellow potassium chromate changing to an orange-red silver chromate. Buckmaster and Gardner have criticised this method, not adversely or unfairly; but it was incumbent to do this, since Nicloux in particular, who has performed much work by this method, regards it as a very exact chemical procedure, and he also believes that results obtained by methods other than this one are too high.

The principal results obtained by the French observers J. Tissot,[1] Mansion,[2] and Maurice Nicloux[3] are described at length in a recent paper.[4] The last observer found that the anæsthetic amount varied for different individual dogs. The same is true for the lethal amount, and the differences between the amount required to produce an anæsthesia in which all reflexes are abolished and the lethal quantity are small. He also found that the quantity of chloroform present in the blood at the anæsthetic stage was almost constant, and independent of the weight of the animal—a conclusion really equivalent to the view that the quantity of blood in the individual does not modify the percentage of chloroform in the blood. Tissot's observations were also carried out on dogs, and the method for determining the amount of chloroform in the blood resembled that employed by Nicloux. The results of Tissot's work showed that anæsthesia can exist with a very low chloroform-content in the blood, and that the amounts in arterial and venous blood differ. During the administration of chloroform the amount in arterial exceeds that in venous blood; during recovery from narcosis more of the drug will be present in venous than in arterial blood. Tissot lays special stress on the point that when mortal syncope or failure of the heart-beat is produced in dogs with a prolonged administration of low percentages of chloroform, comparatively large amounts of the drug are found in arterial blood; but just before actual syncope occurs the amount falls in a marked degree. From this fact he concludes that this diminution in the blood, which is a constant phenomenon, is accounted for by an excessive exit of chloroform from the blood into the tissues of the body, and especially the brain. On this fact Tissot lays particular stress. It is clear, assuming that the experimental data are beyond question, that the cause of death must be ascribed not to a gradual process by which a slow, progressive toxic stage is reached, but to a somewhat sudden change, due to a rush of chloroform from the blood into the body cells; and if this occurs, it will become necessary for us to modify our entire views as to the whole process of anæsthetisation: for other experimental evidence, some of which has been already given, indicates that, with a definite pressure of chloroform in the blood, a definite constant effect is exerted upon the cells of the body. These cannot and do not take up indefinite quantities of chloroform; they take it up in response to a definite solution pressure which exists in the circulating liquids of the body. This remarkable drop in the chloroform-content of the blood we have not observed, though, in view of Tissot's work, the possibility that it might occur was especially considered.

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[1] *Comptes rendus de la Soc. de Biol.*, 1906, pp. 195, 198, 200, 203.

[2] *Ibid.* No. 4, 1906, pp. 206, 238, 241.

[3] *Ibid.* No. 2, No. 3, No. 7, 1906, and November 2, 1907, p. 391.

[4] "The anæsthetic and lethal quantity of chloroform in the blood of animals," by G. A. Buckmaster and J. A. Gardner, *Proc. Royal Soc.*, vol. lxxviii. 1906.

The method pursued by Buckmaster and Gardner in their experiments was as follows: In all cases the percentage of chloroform vapour in the inspired air was determined for each separate experiment. The amount of chloroform in the blood was estimated by the difference in chlorine-content of the blood before the administration of chloroform, and again at any subsequent period from the time when the chloroform-and-air mixture ;was inhaled. The destiny of inhaled chloroform is traced by its chlorine, and the blood during anæsthesia contains an excess of this element. Numerous control experiments were made in order to ascertain whether the percentage of chlorine normally present in the blood of an animal remains sufficiently constant during a prolonged experiment. This was found to be the case when ether was the anæsthetic used. Small amounts of blood withdrawn from time to time during such an experiment were also found to in no way affect the percentage of normal chlorine in blood. The chlorine was estimated by the method of Carius, which is the one generally used for the determination of iodine, chlorine, or bromine in organic compounds. A known weight of blood, about three to five grammes, is treated with nitric acid, and an excess of solid silver nitrate in a bomb tube heated to 200° C. for six hours. The amount of resulting silver chloride was then determined, and the difference between the chlorine-content of the blood before and after anæsthetisation with chloroform was calculated, and this gave a figure which could be expressed as chloroform. The whole method is an entirely new one, and has never been employed by earlier observers. In exactness it is believed to be preferable to those methods where the determination is a volumetric one with an end point which depends upon a colour reaction. Most of these experiments have been carried out on cats, while other observers have generally carried out their investigations on dogs. The chief conclusions arrived at were that the amount of chloroform in arterial blood at the moment when some definite reflex action disappears varies with different individuals. The same is true for the lethal amount in the blood; but a consideration of all the experiments taken together shows that only a narrow margin exists between the weight of chloroform in the blood at the moment of anæsthesia (loss of conjunctival reflexes) and the cessation of respiration (lethal amount).

The above outlines the methods of investigation, and enables the conclusions to be represented in the following table:

Observer.	Animal.	Anæsthetic amount of $CHCl_3$.	Lethal amount of $CHCl_3$.
Gréhant and Quinquaud, 1883.	dogs	50 mg.	...
Pohl, 1890	„	18–50 mg.	35 mg.
Nicloux, 1906	„	50 „	41–70 mg.
Tissot, 1906	„	34–40 „	60–105 „
J. Mansion and J. Tissot, 1906.	„	29 „ 32–43 „	... ...
Buckmaster and Gardner, 1906.	„	16–31 „ reflexes just gone	61–69 mg.
Buckmaster and Gardner, 1906.	cats	14–27·5 mg. reflexes just gone	40 „

From these figures, which are in fair agreement, especially for the lethal dose, it would seem that the quantity of chloroform required to produce various stages of anæsthesia are somewhat higher in dogs than in cats. The difference, however, is not great. The lethal point is fixed as that at which the respiration is of a convulsive type owing to the onset of asphyxia.

THE RATE OF ASSUMPTION OF CHLOROFORM BY THE BLOOD

It is a familiar fact that when chloroform is inhaled the respirations may rapidly diminish in depth and frequency, or even actually stop within a few minutes. In the case of cats it is exceedingly rare not to see this effect on a respiratory tracing. Any individual animal may exhibit this phenomenon in different degrees, and cessation of respiration may be permanent unless resort is had to some means of artificial respiration. Still more interesting is the fact that when the same animal is anæsthetised several times with the same percentage of chloroform vapour, this condition, which may be considered to indicate the first danger point in chloroform anæsthesia, occurs at the same time, and presents a constant type of impaired respiration. During this early period, in about two to three minutes after the administration of chloroform has commenced, a veritable danger point exists, and an elementary account of the physiology of this will be briefly described.

Nicloux points out that during this pre-anæsthetic period the intake of chloroform is rapid even with a low percentage of chloroform in the inspired air. Thus, within three minutes, 56 mgrs. per cent., an amount not much below the lethal quantity, were found in arterial blood when a somewhat large amount of the anæsthetic was supplied. Mansion and Tissot found that when a 4 per cent. chloroform-air mixture is inhaled, arterial blood becomes slowly but steadily charged with chloroform until the content of the drug in the blood is almost identical with the amount of vapour which it can hold *in vitro.* This is about 45 mgr. per 100 grammes of blood for an atmosphere containing 4 per cent. of chloroform (Tissot). After administration of this strength of chloroform, arterial blood contained the following amounts:

After . .	1 hr. 42 m.	1 hr. 50 m.	5 hrs. 15 m.	6 hrs. 56 m.	8 hrs. 21 m.
Mgrs. $CHCl_3$	27	30·5	36·7	42·4	46·2

In the experiments of Brodie and Widdows[1] the rate of absorption of chloroform during the introduction of anæsthesia was ascertained by allowing animals to inhale a known percentage strength of chloroform vapour, 1·06–2·78 per cent. Both the volume of air expired during any interval of time and the percentage of chloroform in this were determined, the latter by the same method which Vernon Harcourt had adopted, which depended upon the combustion of chloroform to hydrochloric acid. The chief new facts elicited by this work show, as might have been anticipated, that the rate at which chloroform is absorbed varies directly with the extent to which the lungs are ventilated. The slow and shallow respirations which occur so early in chloroform anæsthesia also stand in relation with a maximal retention of chloroform in the body, but how much of this is actually in the blood could not be stated. It is, however, abundantly clear that the minimum amount of chloroform in the expired air is found during the second minute, and from that period onwards the amount escaping from the body slowly rises. In a series of experiments, each lasting ten minutes, it was also observed that the amount of chloroform absorbed increased with the concentration of the drug in the inspired air, but the amount was not in proportion to the concentration.

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[1] *Brit. Med. Journal*, July 14, 1906.

In the experiments of Buckmaster and Gardner,[1] which were carried out on cats, small quantities of blood were withdrawn from time to time from an artery during the induction of anæsthesia with known percentages of chloroform vapour and air. The determination of the quantity of chloroform in these samples, ten or twelve in each experiment, afforded the data from which curves could be constructed. In all of the curves the same general features were seen. In the pre-anæsthetic period, or initial stages of anæsthesia, at a time when the individual is conscious, the chloroform-content of the blood rises with great rapidity to a value which approaches a maximum. During this period, which occupies the first few minutes, the first danger point in anæsthesia occurs, because the quantity of chloroform in the blood directly or indirectly affects the respiratory nerve-centres of the brain. In consequence of the respirations being slower and shallower, the amount of chloroform in the blood falls, but the fall is also due to the exit of the drug from the blood into the tissue-cells of the body. When the animal has passed this first stage the amount of chloroform again quickly rises towards a maximum value, and an equilibrium between the factors which determine the amount of chloroform in the blood appears to be obtained, the processes of intake and output of the anæsthetic at the surface of the lung going on side by side. In other words, a state of equilibrium is reached, which persists for a considerable period, and throughout this period the difference between the amount of chloroform present in the blood and what is found at the lethal point is very minute. The state is far from one of safety, and the animal may suddenly die at any moment should any disturbing factors come into play. The whole of this period is a danger period. In the experiments quoted the percentage of inspired chloroform was maintained constant, but it is evident that the contention of those anæsthetists who have insisted that after anæsthesia has been established this can be and should be maintained with a much smaller amount of chloroform vapour, rests upon a sound basis.

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[1] *Proc. Royal Soc.*, B, vol. lxxix. 1907.

Space does not allow of more than a reference to the heart failure which may occur in chloroform narcosis. An inhibition of this organ to such an extent that no blood can be driven through its chambers, though the heart is still beating, may occur at the first danger point of anæsthesia. Particularly valuable work in connection with this has been carried out by Embley,[1] Leonard Hill,[2] and by Brodie and Russell.[3] Studied from the point of view of a reflex action, the last observers have shown that a very close relationship exists between the respiratory tract and those nerve-centres of the brain which control the heart-beat, the respiratory movements, and the bore of the small arteries in the body. The most sensitive surface which, when stimulated, reflexly affect these centres is that of the lining of the nose, next the mucous lining of the larynx, and then the surface of the lungs, which are powerfully stimulated by vapours of chloroform, formaldehyde, and bromine. When the internal surfaces of the trachea and bronchi are irritated no reflex of the type just described can be evoked. Stopping of the heart alone is very easily brought about as a reflex action by stimulating the pulmonary branches of the vagus. The experiments of Embley have shown that for dogs the first danger point, cardiac inhibition, and consequent slowing of the respirations, can be entirely set aside by removal of the heart from the influence of the centres in the brain by cutting the two vagi nerves along which the impulses which check or arrest the heart normally pass. The effect of atropin, which cuts out the inhibitory influence of the vagus upon the heart, has been re-investigated by Schäfer and Scharlieb,[1] who have suggested its employment prior to chloroform anæsthesia. Embley and F. J. Martin[2] have also demonstrated the toxic effect of chloroform upon the unstriped muscle in the walls of the blood-vessels. These dilate when perfused with blood charged with a small percentage of the drug.

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[1] *British Medical Journal*, April 5, 12, and 19, 1902.

[2] *Ibid.*, April 17, 1897, and December 1900.

[3] *Journal of Physiology*, xxvi. 1900.

THE FUNCTION OF THE RED CORPUSCLES IN CHLOROFORM ANÆSTHESIA

Schmiedeberg was of opinion that the red corpuscles were the chief vehicles in the transport of chloroform from the lungs. This was supported by Pohl's experiments, and Nicloux, who used centrifugalised oxalated blood removed from a vein, recovered 64·4 per cent. of the chloroform in blood from the red corpuscles and 13·3 per cent. from the plasma. His figures for the distribution of chloroform among the constituents of the blood are much below those of Pohl, who had stated that 87-90 per cent. of the total chloroform was held by the red corpuscles; in other words, the chloroform-holding power of the corpuscles is seven to eight times that of the plasma.

Experiments undertaken by Buckmaster and Gardner, in order to ascertain how the anæsthetic distributes itself in the blood between the corpuscles and plasma, proved to be exceptionally difficult.[3] The separation of the corpuscles was accomplished by centrifugalising tubes of blood surrounded with ice, so as to hinder any clotting. Their conclusions, that chloroform is very firmly held by the blood of an anæsthetised animal, are in accord with all other observers. But it was also found that chloroform primarily associates itself with the red corpuscles and does not enter the plasma to any marked extent unless the anæsthesia is pushed to an extreme degree, or a chloroform-and-air mixture is administered with a high percentage of the drug. At the period when the reflexes disappeared the percentage of chloroform in the red corpuscles was found to be 64·3 per cent.; in another case 71·1 per cent., and after the inhalation of 2 per cent. chloroform for three quarters of an hour no less than 98·5 per cent. of the anæsthetic was held by the red corpuscles.

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[1] *Trans. Roy. Soc. of Edinburgh*, vol. xli. Part II. (No. 12).

[2] *Journal of Physiology*, xxxiii. 1905.

[3] *Proc. Royal Soc.*, B., vol. lxxix. 1907, p. 566.

In order to obtain additional proof that the red corpuscles, as would seem to be the case from the above experiments, are the essential vehicles for the carriage of chloroform, Buckmaster and Gardner argued that if the view was correct that the transport of chloroform was a function of the red corpuscles, then, though the absolute amount of chloroform present in the blood might be modified by abstracting or adding blood from or to an animal, the *percentage of chloroform* ought to remain constant.

The general plan of the experiments was to anæsthetise an animal with ether or nitrous oxide, allow the anæsthetic to be disengaged from the body, and then administer a known percentage of chloroform. The determination of the amount of the drug in the blood was made at the asphyxial point. In one hour or an hour and a half all the anæsthetic was eliminated, and during this period a measured amount of blood was abstracted and the experiment repeated. In other experiments the amount of chloroform present was determined in the same animal before hæmorrhage, after hæmorrhage, and after the replacement of the blood which was furnished from another animal in such quantity as to augment the original volume of the blood by one-third to one-half.

The general results of all the experiments will now be detailed.

	Average amount of $CHCl_3$ per 100 grammes of blood.	
	Before bleeding.	**After bleeding.**
Experiments in which the asphyxial state was rapidly reached, in about 3 to 9 min.	0·043 mg.	0·045 mg.
Experiments in which the asphyxial state occurred in about 30 to 80 min.	0·048 „	0·051 „

	After hæmorrhage.	**After replacement of the blood.**
Experiments made at the asphyxial point.	0·0421 mg. 0·0768 „	0·0426 mg. 0·0768 „

	Before hæmorrhage.	**After hæmorrhage.**	**After replacement of blood.**
Experiments made at the asphyxial point.	0·061 mg.	0·059 mg.	0·049 mg.

From the above it would appear that the conclusion is justified that the percentage of chloroform in the blood does not undergo any variation corresponding to differences in the volume of the circulating blood, and this is what was to have been expected if the red corpuscles were the essential agents for the transport of chloroform. It may be considered in the highest degree probable that the anæsthetic is associated with the proteins of the corpuscle, but the experiments naturally give no clue as to whether it is the hæmoglobin or other cell-proteins which actually pick up the drug. The earlier work of Hedin, Overton, G. W. Stewart, and Oker Blom, among others, on the permeability of the red corpuscles is of considerable importance in connection with the association of chloroform by the corpuscles. Stewart has pointed out that as far as certain electrolytes are concerned the permeability of the envelope alone, or of the whole disc, is dependent not on the life but on the structure of the corpuscles, for these, under a variety of conditions which are incompatible with life, and when the hæmoglobin is converted into methæmoglobin, preserve their permeability to some substances, but remain relatively impermeable to the electrolytes of the plasma. Hedin's experiments have demonstrated that some substances, such as sugar or sodium chloride, are unable to penetrate the corpuscles, while substances like urea, antipyrin, and the narcotic urethane easily enter them. The group of aldehydes, ketones, and alcohols, many of which affect the organism like the better known anæsthetics, if added to blood are found to be so distributed that nearly all the added substance is found in the red corpuscles. The significance of such experiments is great, for it establishes the fact that alcohol, or a narcotic, like urethane, can, and actually does, enter the cells of the body.

The Rate at which Chloroform is eliminated from the Blood after Anæsthesia

All observers are agreed that after the supply of chloroform is stopped the anæsthetic rapidly leaves the body. Five minutes after anæsthesia half the amount in the blood had disappeared; 7 milligrammes were found three hours later, and by the seventh hour the blood became free from chloroform (Nicloux). Tissot suggests that a study of the amount of chloroform in arterial blood should be made during the induction of anæsthesia, but that determinations of the chloroform-content of venous blood are necessary if we are rightly to understand the rate at which it is eliminated. According to his experiments, the amount of the drug in venous blood constantly exceeds that in arterial during recovery from chloroform narcosis. Expressed in other words, directly the administration of the anæsthetic ceases the cells of the body begin to discharge their associated chloroform, and with this their functions gradually become restored. The subjoined table from one of Tissot's papers is of interest:

	Milligrammes of $CHCl_3$ per 100 grammes of blood.		
	Chloroform administration stopped.	45 min. later	2 hr. later.
Arterial blood . . .	53·2	5·8	0
Venous blood . . .	48·1	7·7	4·9

In our own experiments,[1] immediately the inhalation of chloroform stopped, a sample of blood was taken from an artery, and this was repeated at intervals, until half or three-quarters of an hour had elapsed. In other experiments venous blood taken close to the right ventricle of the heart was examined in the same way, while in a few experiments samples of arterial and venous blood were taken simultaneously. The main conclusion which can be drawn from these experiments is that the rate of elimination of the drug from the body *viâ* the blood depends upon the physiological state of the individual animal. The rate of loss is at first comparatively rapid, and subsequently becomes slower. But the initial rates of elimination are much less rapid than the initial rates of the intake of chloroform, and, on the whole, elimination is a much slower process than assumption, a view which is supported not only by the actual determinations of chloroform in the blood but by a comparison of the times at which the various reflexes disappear and reappear. From our curves the initial falls are not quite so rapid as the work of other observers had led us to suppose. The chloroform-content of the blood was only reduced by 50 per cent. in 15 to 20 minutes; three-quarters of the chloroform was eliminated in about half an hour. These statements hold good when the animal is breathing naturally, but, as might have been expected, the extent to which the lung is being ventilated during any period is the chief, if not the only, factor which determines the rate of elimination. Our experiments are in agreement with Tissot's observations, that at the moment when chloroform inhalation stops arterial blood contains an excess of the drug when compared with venous blood, but the difference between the amount of chloroform in arterial and venous blood after regular respiration is established is practically the same.

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[1] Buckmaster and Gardner, *Proc. Roy. Soc.*, B., vol. lxxix. 1907.

A sufficient and satisfactory explanation of the anæsthetic process probably cannot be given at present, but some conception of the anæsthetic state produced by the inhalation of chloroform vapour at about 2 per cent. may be attempted. It is true that data for this have been obtained by experiments on cats, but it is allowed that the phenomena shown by this animal during anæsthetisation closely resemble what is seen in man. The blood at first rapidly becomes charged with chloroform, which is held almost entirely by a protein or proteins of the red corpuscles. The respiratory centre or centres are at first stimulated, but these become affected quite early, and then discharge pulses less frequently and less efficiently than in a normal animal. In the dog especially, and to a less extent apparently in the cat, this behaviour of the centre is secondary to a weakening, or almost a cessation, of the activity of the heart. From this inhibitory effect the heart escapes, somewhat easily in the cat compared with the dog. The condition just described occurs early, within the second to the fifth minute, and may be considered as the first danger point in anæsthesia. In consequence of the slow and shallow respirations, the percentage of chloroform in the blood falls, either owing to a diminished intake of vapour or to the cells of the body storing up the drug at the expense of the blood, or because the elimination of the drug is as rapid, or more rapid, than the assumption. But the last cannot be the explanation, for the rate of elimination is by no means so rapid as is the assumption. The fall is, therefore, due largely to the disappearance of chloroform into the cells of the body, which, in virtue of their proteins, are capable of forming loose chemical combinations or aggregations with the drug. The cells are, in consequence, poisoned in varying degree. When the first danger point is safely passed, the respiratory movements improve in frequency and vigour, and this may be considered to represent a continuation of the initial stimulating effect of the drug, which was masked by the occurrence of a danger point. Thereafter the chloroform-content of the blood quickly approximates to a maximal value, which is maintained until asphyxial convulsions occur. This may be termed the second danger period. The difference between the chloroform-content of the blood at the initial period, when the first danger point is reached, and also at the maximal value, when compared with the lethal amount, is very minute. The quantity of the drug in the blood governs the distribution of the anæsthetic which at first stimulates, and then finally paralyses certain cell districts of the body in definite order. Chloroform, therefore, though a toxic substance, does not produce its effects upon the organism by a cumulative action; these are not dependent upon the absolute quantity which is supplied, but upon the percentage-value of the drug in the blood stream.

THE REFORM OF THE MEDICAL CURRICULUM (II)

BY PROFESSOR HENRY E. ARMSTRONG

ANOTHER act in the drama of medical education was recently played to a finish when the Senate of the University of London, at its November meeting, decided that it was unable to evolve a constructive scheme which would render possible the use of the great gift offered for the establishment of a school of preliminary medical studies at South Kensington. Like the truth, jealousy has prevailed: London seems to be ever at the mercy of contending factions—a natural result, perhaps, as she altogether lacks leadership.

I am constrained therefore to continue the article on the reform of the medical curriculum which I contributed a little more than a year ago to this journal and which, meanwhile, has met with a rejoinder from Dr. Wade (No. 4, April 1907).

Dr. Wade and I are obviously looking at things from different points of view: his being that we are living under almost ideal conditions, which cannot well be changed and which need not be changed; mine that we are in a time of makeshift: that it is our duty to take stock of the situation, to mend our ways without delay. Thinking that all is for the best in the best of possible worlds, he would pursue a *laissez-faire* policy. My desire is to see a new point of view introduced into the subject: it seems to me that it is useless to attempt to teach chemistry to medical students except as the study of function—the study of processes. Unless they can more or less understand the nature of the chemical processes which occur normally and under pathological conditions, as well as in some measure appreciate the alterations likely to be effected by changes in the conditions, they cannot possibly penetrate behind the veil which Nature at present draws in front of them.

I believe medical opinion will be with me; that many will agree with me that the preliminary studies, as at present conducted, afford neither systematic scientific training nor proper technical training, the memory being merely loaded with a vast mass of uncorrelated facts, some of which, of course, are of interest and value: in the main, however, the time spent in acquiring them is ill spent, as a false direction is given to the mental activities. To give an example—happening recently to mention *Cholesterol* to a sharp young medical student now following the clinical course, I met with the pat reply—"Oh yes, that is the stuff in Lanolin: a monatomic alcohol, crystallising in rhombic plates with a bit snipped out of one corner, which gives a fluorescent red coloration with strong sulphuric acid." "Knowing that," said I, in amusement, "you must feel that there is nothing more to be learnt on the subject and that you are provided for life with information of inestimable value." "With information," said he, "sufficient probably to make the difference between passing or failing in the Second M.B." (at Cambridge). This illustrates, not inaptly, the present-day attitude, the kind of knowledge which it is thought is essential —and which is taught as essential.

It is worth while to examine Dr. Wade's case somewhat in detail. In discussing my qualifications to act as critic, he implies that I have taken an interest only in elementary school affairs and pictures me as a sort of educational Rip van Winkle, returned to the scene of my early labours with rusted barrel and decayed stock, unable to divest myself of old memories—thinking only of medical education as it was in the days when I took some direct part in it: the days of blackboard demonstration without practical illustration. I can scarcely think of myself as so entirely decadent. Like that contraption the Tar Baby, I may have worn the appearance of a mere scarecrow in medical eyes. Brer Wade forgets, however, that it is possible to lie low with eyes open; like Brer Rabbit, to take notice of all kinds o' persons, keeping the old woman at hand watching the kettle on the fire, in readiness when the time comes to pour down the "bilin" water on Brer Wade and his friends, practice having been gained meanwhile by spilling some of it on schoolmasters' heads.

Feeling as I always have and still do that a solid foundation is the first requisite, I have done my best to promote the introduction into schools of teaching calculated to develop some understanding of scientific method. Some little progress has been made and in the last years of the old University of London, partly perhaps owing to my representations, some pressure was being brought to bear on the schools to make such teaching rational and effective. One of the first acts of the newly constituted University—one of its most retrograde and unforgivable acts—was to undo the good work of its predecessor. The protests made by those of us who had experience of the value of the system under which some knowledge of science was required of all at Matriculation were unheeded; we were advisedly excluded from all Committees dealing with such matters, and freedom to neglect their duty was conferred upon the schools preparing candidates for matriculation. Freedom, we all admit, is good in the abstract—but freedom is easily abused by those who are not ripe to enjoy it: for the most part, the schools were incapable of running alone—they were and still are in need of guidance.

Men like Dr. Wade apparently do not realise the truth of the adage that there are more ways of killing a pig than sticking it—that it is policy sometimes in hunting to approach your quarry in indirect ways—that there may easily be more haste and less speed—that it is well sometimes to play a waiting game, to exercise purpose silently. His present experience as a teacher of medical students is not very much greater than mine was when I gave up such work; since then I have been steadily engaged, I regret to say during five-and-twenty years, in educational research work—constantly making experiments, constantly thinking over and discussing the problems of education. My wits have been sharpened the more in that I have enjoyed an opportunity which has fallen, I think, to no other teacher of chemistry quite in the same degree—that of developing courses for and ministering to the wants of large special classes of students not destined to follow a chemical career, engineers mostly, first at the Finsbury Technical College, then at the Central Technical College. This more than anything else has led me to appreciate the possibility of teaching a subject in relation to its technical uses. I venture therefore to suggest that Rip has been active in retirement, not asleep; that he is down from the mountains by no means unfit for the fray.

And in other ways the course events have taken has been such as to impress me with a sense of the gravity of the situation. But a few months after I commenced to breathe an atmosphere of apomorphine[1] at St. Bartholomew's Hospital Medical School in 1870, my chief Matthiessen came to an untimely end. I discovered him, one afternoon, asleep for ever, in his armchair: my first experience of real life—in itself an event to make a young man think. Had he lived, Barts might well have been made the centre of research on alkaloids and their use in medicine, a centre of inspiration—as he was a man of indomitable energy, full of scientific enthusiasm, with an extraordinary faculty of choosing workers and making them work; he had too the gift of insight and was interested in things organic and inorganic; in fact, he was a complete chemist in feeling: one who could determine electrical conductivities without lapsing into ionomania and who would have set his face against unreal, pretentious talk on the subject. His work on narcotine with Carey Foster and Alder Wright practically laid the foundations of alkaloidal chemistry. Whenever a chance comes to us in this country, however, we seem to let it lapse: lack of scientific training and of the scientific spirit has led the medical profession to overlook the advantages accruing from systematic research work, and the development of a narrow humanitarian spirit among the public now threatens to put a complete stop to such work in medical schools, as the hospitals are held to exist solely for the cure of poor patients: the number of persons, poor and rich, is in no way thought of who die lingering deaths because of our neglect to carry on systematic inquiry in directions likely to be of benefit to medicine. The chance once in the hands of Barts, thoughtlessly sacrificed, will not soon occur again, I fear.

In my former article, I spoke of a just feeling among medical men "that the present course in chemistry is a totally unfit preparation for medical practice"—and added: "this is the feeling we have to meet and provide for." Dr. Wade notwithstanding, I still affirm this to be the case, and I have reason to think that the teaching of other preliminary subjects is more or less open to similar criticism.

He has represented me as having made "an attack" on the curriculum of the University of London—in reality, my remarks were of general application, the condition of schools outside London being at least as unsatisfactory as that of those in London.

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[1] Apomorphine was then under investigation and was in the air in more senses than one.

I have led the reader who is unacquainted with the subject to believe, it appears, that medical education has remained unaffected by the rapid march of science during the past fifty years—actually I drew attention to the many improvements effected even during my time.

My remarks, Dr. Wade considers, might lead readers to believe that our whole system is radically wrong—they were intended to have that effect.

That the issue will be fraught with disaster unless the curriculum is remodelled, I have no doubt: it is already, in fact. Men are dying on every side owing to our inability to apply chemical knowledge to the interpretation of disease. Such homicide, however unwilful, must none the less come to be regarded as unjustifiable, if a consequence of ignorance which it is in our power to overcome. And it is in our power to overcome it, at least partially.

A stern duty may also lie before medical men for which they will have to be prepared. Many are living whose existence perhaps is a matter of extreme danger to the State, as the perpetuation of their kind may be expected to have the most serious consequences. The problems of heredity need consideration from this point of view; unless medical men can undertake their study and act as advisers of the public, society will not receive that protection which sooner or later it will come to expect from the medical profession.

Although surgeons have advanced their practice by leaps and bounds, that of medical men has almost stood still: the great improvements—such as the treatment of rabies and diphtheria by appropriate antitoxins and the various new potent drugs, not forgetting lumbar anæsthetics—are due to chemists. The fact is the medical man is not sufficiently versed in scientific method to undertake the diagnosis of the obscure phenomena of chemical change in the complex material which constitutes the human body. He understands but few simple chemical changes occurring in test tubes—the complexities of change under vital conditions are entirely beyond his ken and grasp.

The case is well stated by Archdall Reid in the following passage (*The Principles of Heredity*, 2nd ed. 325):

> The principal aim of that part of formal education which is not specially intended to supply the individual with useful knowledge should be to develop his reflective powers. Much scientific teaching as practised at present does not fulfil this condition. For example, the medical profession includes the largest number of scientific men in the world. From first to last during his career the medical student is loaded with a monstrous and ever-increasing burden of facts, but no systematic effort is made to increase the acuteness and range of his thinking processes. A great deal of the burden on his memory is necessary; but not all of it. Thus since he treats the ailments of an animal, man, largely by means of vegetable drugs, he is taught botany and zoology. In botany he learns such things as the peculiarities which distinguish various natural orders of plants from other natural orders. In zoology he acquires a more or less elaborate knowledge of the structure of certain types of animals—the vascular system of the sea-urchin, the organs of generation of the earthworm, the skeleton of the frog, the bones of the cod's head, the dentition of the different species of mammals and so forth. But no man is a better physician for knowing the difference between a raceme and a rhizome, nor a better surgeon because he has studied the anatomy of the cockchafer. His subsequent experiences do not link up with these fragments of knowledge which, though necessary to the equipment of the professional botanist and naturalist, are so remote from the labours and interests of the medical career that presently they are forgotten. In the end the average doctor has a knowledge of botany and zoology not much more profound nor useful intellectually than that possessed by the average farmer or stockbreeder. Either he should be otherwise employed during his earlier studies or his later work should be so modified as to link up with them. Facts, scientific or other, have by themselves no intellectual or scientific value. It is the recognition of the relationship between facts in a natural group and between different groups that confers the value. No doubt medical students, in proportion to their intelligence, get a general notion of the essential likenesses, which, amid distinguishing differences, bind together all living nature. But this result, if it be the one sought, is attainable by direct teaching at a hundredth part of the cost in time and labour.

It is the misfortune of the public as well as of the medical man that he is placed in this position. And to him before all others it is of importance to remove the disability from which his profession undoubtedly suffers. He can help more than most if he care to act—as there can be little doubt that the public would be advised by him. The clergy no longer count in education—as a body they have ceased to take an interest in the subject, and their interests are thought to be so opposed to those of the modern scientific school that they are not likely to intervene on behalf of training the value of which they are entirely unable to appreciate. It is the more important, therefore, that medical men should recover the position they formerly held in common with the clergy, as men of culture.

In defending myself against the charge of being asleep—as Dr. Wade suggests that my allegations are vitiated by inability to divest myself of old memories—I may not unfairly point out, perhaps, that my critic is not yet awake to possibilities which I seem to see clearly. His conservative attitude is in itself proof that he is scarcely qualified to enter on a discussion such as we are now engaged in. His connection with the subject of medical training arises rather from his being in a medical school than of it. Apart from his obvious lack of feeling on the physiological side, in common with so many other chemists he in no way realises apparently how vast is the change which has come over chemistry within recent years, making it possible to teach the subject far more effectively than formerly. Herein lies the difficulty. Our brains are addled by the constantly increasing load with which we weight ourselves. Very few can see their way out of the wood for the trees. We do not even know how to use books effectively and insist on our students learning off everything by heart instead of teaching them to understand principles and economise effort by referring to their books for detailed information when occasion arises.

Dr. Wade argues that the teaching is enormously improved. Formerly, he says, the scientific spirit was absolutely destroyed by blackboard demonstrations without experimental illustrations and no opportunity was given to the student of verifying his teachers' statements: it is quite otherwise now. Is it? Does the average student gain much from seeing a few practical demonstrations in the course of a lecture or from preparing a few substances in the laboratory? I doubt it. The intelligent man in the old days learnt from lectures practically as much of things essential as the intelligent man does in these days: then as now far too much attention was paid to mere fact knowledge, to the kind of fact which comes into prominence, for example, in Dr. Wade's own book—of its kind, a very admirable one—or as illustrated above by the reference of my young student friend to cholesterol. The one real improvement in the course is the introduction of simple quantitative laboratory work, such as I pleaded for in my B.A. address in 1885—conceptions are established in the mind of the student by such work which are invaluable.

Instead of dealing with irrelevant matter, says Dr. Wade, the proximate constituents of the food, degradation products of the body, urea, etc., are considered. The same were dealt with in my day. The question is—How are they dealt with—any more usefully than formerly? I doubt it. Murder will out, and out it comes when Dr. Wade tells us that "Chemistry for medical students bears precisely the same relation to physiology and pathology as anatomy does, the chemist dealing with the nature and relation of the materials and the anatomist with the nature and relation of the structures the function of which, in both cases, it is the part of the physiologist to investigate." Chemistry as thus defined by Dr. Wade is a kind of dry-bones business—and so it usually is; the chemistry the medical man needs, however, is not for the most part anatomical but functional: physiology, therefore, in a large measure, overlaps it. This is what Dr. Wade and his friends do not see—but they must come to recognise it, sooner or later.

Students, in his laboratory, says Dr. Wade, dissect chemically and, where possible, reconstruct artificially, compounds such as urea. Suppose they do—how much better off are they? As ordinarily conducted, the exercise is an almost worthless one, in my opinion. And from a medical point of view, it doesn't really matter what urea is: a harmless waste product, containing oxygen and nitrogen in their lamest form, its importance is generally much overestimated in chemical circles, just as we now have reason to suppose it was by Fick and Wislicenus, who spent much unnecessary effort on the Faulhorn in worship of its supposed functional significance. The student does not really dissect it when he gets ammonia, etc., from it any more than an anatomist dissects a bone when he gets calcium phosphate from it; probably, moreover, urea is not what he is commonly taught to suppose it is—*carbamide.* Long absorbing conversations which I had with Peter Griess—the prince of nitrogen chemists—in days of yore rise in my memory when I write this: he would not listen to its being called carbamide.

The really important problems centring around urea are not taught—the wonderful inter-relationship of the closely allied forms of the compound CON_2H_4; the condition of equilibrium in which urea, carbamide and ammonium cyanate subsist in solution: although probably of high physiological importance, these subjects are considered to be far too difficult for the medical student to tackle; really they are the points which he should be led to study very thoroughly. From the medical point of view, the substances which accompany urea in urine in fluctuating proportions are far the more important —as they are often of diagnostic value.

If those to whom I am addressing myself scarcely grasp the force of this argument, they will nevertheless see, assuming my contention to be correct, that the suggestion that chemistry is taught in medical schools in an unsympathetic manner cannot be so far from the truth after all!

Dr. Wade altogether objects to the proposition that we might well give some consideration in the first instance to complex cases, such as the processes of digestion, for example. From the objection he makes, it is clear that he in no way appreciates the marvellous advance made in this field of late years. Knowing as we do now the fundamental importance of enzymic action both in up-grade and down-grade processes, it is clearly our duty to make this a primary subject of study. Colloid substances also invite special attention and such simple substances as water, which now is scarcely considered, although physiologically perhaps the most important constituent of the body; what is taught about it—its composition, etc.—is worthless for all practical purposes.

According to Dr. Wade, present-day examinations in science are very different from and better than those held when I taught medical students. They are absolutely the same, except—and the improvement is a real one—that simple quantitative exercises have been introduced into the practical chemistry examinations. When I contrast the questions set last year with those set twenty-five years ago, I find no difference: the same stock academic riddles are propounded year after year. At no time have the questions had any real bearing on the problems which face the medical man; those set during the past year or two are as futile as those which I assisted in setting in the early 'nineties, although meanwhile, as already pointed out, there has been a vast development of knowledge.

The main lines on which chemical change proceeds having been made clear to us, there is no question that it is now possible to teach a chemistry which should give eyes to the medical man and enable him gradually to pierce the gloom which still enshrouds the subtler changes: I therefore contend that we are much behind the times.

Dr. Wade not only says that chemistry is now taught (in the London Medical Schools) with direct reference to its scientific application in physiology and medicine, but that the curriculum laid down for medical students has been specially constructed and, except in the purely elementary parts, is essentially different from that laid down for chemical students. Let us see if this be so. I take the following first year's course of study from the Regulations (issued in September 1907) in the Faculty of Medicine for Internal Students:

Inorganic Chemistry

The *Curriculum* in Chemistry shall consist of not less than sixty Lectures and one hundred and twenty hours' Practical Work in the course of an Academic Year. The Syllabus is as follows:

I.—For Lectures

Illustrations and examples of chemical action. Solution, crystallisation, distillation, sublimation, precipitation. Mixtures and single substances, separation and decomposition.

Gaseous and liquid diffusion.

Indestructibility of matter. Elements and compounds. Laws and condition of chemical action.

The atomic theory. The determination of molecular weights, equivalents and atomic weights. Valency and structural formulæ. Equations. Chemical calculations.

Classification of the elements, including the periodic system. Synthetical production of compounds from their elements. The general characters of the chief types of compounds. Acids, bases and salts. Chemical nomenclature and terminology.

The principles of gravimetric and volumetric analysis.

Production and properties of the more important and typical elements and of their most familiar compounds.

The character of chemical changes, including the study of simple exothermic and endothermic reactions, thermal dissociation, electrolysis, catalysis, mass-action and rates of reaction; the conditions which determine and influence such changes and the attendant phenomena. Osmotic pressure.

The above to be illustrated by a detailed consideration of the following:

Oxygen, Nitrogen, Hydrogen.—Chemical nature of the atmosphere; composition and properties of water; natural waters; the oxides of nitrogen; nitrites and nitrates; ammonia, ammonium salts, hydroxylamine; hydrogen peroxide, ozone.

Carbon.—Its oxides, carbonates; relation of carbon dioxide to animal and plant life; carbon disulphide; coal and coal-gas; combustion; nature of flame; cyanogen, hydrocyanic acid and the metallic cyanides.

Fluorine, Chlorine, Bromine, Iodine.—Their compounds with hydrogen; oxides of chlorine, hypochlorites, hypobromites, chlorates, iodates.

Sulphur and Phosphorus.—Their compounds with oxygen and hydrogen; chlorides of phosphorus; sulphides, sulphates, sulphites, sodium thiosulphate; phosphates.

Boron and Silicon.—Their oxides; boric acid and borax; silicon fluoride; nature of glass.

Occurrence in nature, sources and preparation of the following metals and their principal compounds, omitting metallurgical processes: lithium, sodium, potassium; calcium, strontium, barium, magnesium, zinc, cadmium; copper, silver, mercury; iron, aluminium, chromium; manganese; lead, tin; arsenic, antimony, bismuth.

(N.B.—The whole subject will be treated in an elementary manner.)

II.—For Practical Work

The Course must be such as will enable Students—

(*a*) To prepare and demonstrate the properties of common metallic and non-metallic substances and to purify them by precipitation, crystallisation or distillation.

(*b*) To perform accurately the following simple quantitative operations: the determination of the equivalents of copper by reduction of its oxide and of copper, tin and zinc by oxidation; alkalimetry and acidimetry; the estimation of chlorides gravimetrically and by titration with silver nitrate; and determinations involving simple applications of the permanganate and iodine thiosulphate processes.

(*c*) To identify by simple tests the common elements and their more familiar compounds, including mixtures which may contain not more than one acid and two metals belonging to different analytical groups.

(*d*) To write out a clear account of their practical work, accurately describing the nature of the processes employed and, where possible, representing by equations the chemical changes involved.

To my thinking, the course here laid down is an ordinary, thoroughly old-fashioned and conventional preliminary course of inorganic chemistry. There is not a single word to indicate any connection with either physiology or medicine. It scarcely differs from the 1890 scheme, except in the practical part, *a* and *b* in this being new: (*b*) is admirable in principle: the improvement in teaching, to which Dr. Wade refers, in my opinion is due to its introduction; what (*a*) may or may not mean it is difficult to say.

The current scheme for chemistry in the Faculty of Engineering is as follows:

The methods which lead to the discovery of the composition of common materials occurring in nature.

The determination of molecular weights, equivalents and of atomic weights. Valency and structural formulæ.

Classification of the elements, including the Periodic Scheme.

General characters of the chief types of compounds, including acids, bases and salts and a few prominent carbon compounds, especially as illustrating the relations of properties to composition and structure. No distinction will be admitted between Organic and Inorganic Chemistry.

History, production and properties of the more important and typical elements and their most familar compounds.

The character of chemical changes, including combustion, thermal dissociation and electrolysis; the conditions which determine and influence them and the attendant phenomena.

The whole to be treated in an elementary manner.

Tersely worded as it is, this is infinitely superior to the medical scheme as a statement; but it is essentially the same scheme; not essentially different from the latter. The fusion of organic with inorganic chemistry, which Dr. Wade speaks of as having been tried with disastrous results, is treated, it will be noticed, as an accomplished fact.

Passing to the second year's course, we have the following:—

The *Curriculum* in Organic Chemistry shall consist of not less than sixty Lectures and sixty hours' Practical Work in the course of an Academic Year.

The Syllabus is as follows:

I. FOR LECTURES

1. Purification of solids and liquids.

2. Analysis of organic compounds. Estimation of carbon, hydrogen, nitrogen, sulphur, phosphorus and the halogens.

3. Empirical and molecular formulæ. Determination of molecular weights.

Students will be expected to know the general properties of the following groups of compounds, illustrated in each case by reference to a few of its more important members:

Aliphatic Series

Paraffins (especially methane and ethane).

Unsaturated hydrocarbons (especially ethylene and acetylene).

The different classes of alcohols and their derivatives (with special reference to methyl alcohol, ethyl alcohol, glycerol and mannitol).

Aldehydes (with special reference to formaldehyde, acetaldehyde and chloral hydrate).

Ketones (with special reference to acetone).

Acids (with special reference to formic, acetic, lactic, oxalic, succinic, malic, tartaric and citric acids).

The preparation and properties of the following derivatives of acetic acid: acetyl chloride, acetic anhydride and acetamide.

Simple ethers (with special reference to ethyl ether).

Esters (with special reference to ethyl acetate and saponification).

Amines. Amido-acids. Glycocoll.

Carbohydrates. Sugars (and more especially glucose, fructose, lactose, maltose and cane-sugar). Starches. Glucosides.

Cyanides. Urea. Uric acid.

Aromatic Series.

Hydrocarbons: benzene, toluene and their simple derivatives.

Sulphonic acids.

Phenols (with special reference to phenol, catechol, hydroquinone and resorcinol).

Benzyl alcohol. Benzaldehyde.

Acids. Benzoic acid. Salicylic acid.

Pyridine.

(N.B.—The whole subject will be treated in an elementary manner.)

In 1890, the Organic Intermediate course was as follows:

The composition, the properties and reactions and the more important derivatives of the following substances:

The principal series of Hydrocarbons (with special reference to their chief Haloid and Nitro-derivatives).

The Ethylic series (with special reference to ethers, esters or ethereal salts, aldehydes, ketones and acids).

Glycol. Glycerine; natural fats.

Amylaceous and Saccharine substances.

Vegetable acids.

Benzene and Toluene with the principal Phenols and Nitro-derivatives.

Ammonias and the more important natural Alkaloids.

Amides, Urea, Uric Acid.

Cyanogen, Cyanides, Cyanates and Cyanurates. Glucosides.

The processes of Saponification and Fermentation.

The principles involved in Ultimate Organic Analysis and in the determination of Molecular Weight.

Again, the difference is merely nominal, except in the practical work, which is now slightly superior to the old pass but inferior to the old honours examination, as this included the volumetric Pharmacopœia work. It is noticeable that hydrolysis and fermentation could be examined on in 1890 but that the latter is now left out, although of infinite importance from a medical point of view. Evidence that the subject should be taught with direct reference to its scientific application in physiology and medicine can only be found in the entire absence of reference to this desirability. Indeed, with such syllabuses in operation, the authorities have no right to expect any special knowledge of medical applications from candidates—and the examination papers show that the examiners are either alive to this fact or are unable to deal with the medical aspects of the subject.

In the true school of the future, teachers will not be restrained by stereotyped syllabuses; they will teach what is necessary without reference to any narrowing schemes such as are now forced upon them by persons who have no proper understanding of the actual work. The syllabus is always a compromise and representative of mediocrity; it never reaches the high-water mark of experience in a subject.

It will be noted that the time prescribed for laboratory work in both years is only twice that to be devoted to lectures. Whether the time be sufficient or not need not be considered; it is certain, however, that long courses of lectures are now thoroughly discredited as a means of giving elementary instruction.

Turning now to the consideration of the future, the task before us is clearly that of rendering our Universities efficient as educational machines; at present, they are almost beneath contempt as such, owing to the lack of effective organisation—to the lack of true ideals and of active co-operation among their workers; so much is this the case that they may be said to exemplify human frailty rather than human faculty. Taking London as an example, the whole of the University organisation proper is practically worthless, except as a means of retarding progress: the only useful parts are the individual Schools; instead, however, of recognising the importance of these and facilitating, improving and harmonising their work, the University machinery is made use of mainly as a means of stultifying their efforts—the attempt being made persistently to reduce all to one dead level of uniformity.

Dr. Wade is one of those who at the last senatorial election took a prominent part in depreciating the efforts that are being made to develop systems of training suitable to the times by allowing himself to become an advocate of the policy of the Graduates Association. The professed object of this Association is to maintain a rigid, uniform system of examinations for so-called external and internal students alike; and its professed policy is one of antagonism to the teachers in the schools. Of course, the contention is that the agitation is on behalf of the maintenance of a pristine standard, which is painted as having been a very high one—but those who defend this position forget to inquire whether the standard may not have been merely one of difficulty rather than one of excellence; they at least quietly, if not advisedly, ignore this possibility. Those who are behind the scenes know full well that excellence is not thought of. The struggle is between two systems: the one being that of the Schools—in which the attempt is being made to develop practical methods of teaching, having practical ends in view; the other being that of the Coaches—whose object is to secure the immediate success of their pupils at the examinations. The issue will be determined by public decision in favour of one system or the other: the public must determine whether its interests are best served by a system which, if properly administered, cannot but afford training likely to promote efficiency; or by one which tends rather to the stultification of faculty, its end being the immediate, always more or less faulty solution of a series of Chinese puzzles having no relation to the requirements of life, not competency and skill in doing actual work.

The University machine must be made sound in its working parts, if it is to run smoothly and effectively.

> "What's the good of Mercator's North Poles and Equators,
> Tropics, Zones and Meridian Lines?"
> So the Bellman would cry; and the crew would reply,
> "They are merely conventional signs!"

And so it is with the Senates, Faculties, Boards of Studies and all other such institutions—for the most part, they are mere time-wasting contrivances; the Schools are the one essential feature of the University organisation: if they are guided by true ideals and in honest hands, they may be counted on to do effective work—not otherwise: no mere ordinances can help them; suspicion of the teachers can only nullify their efforts.

To put the teaching of the preliminary medical subjects on a sound basis in London, the first thing to do is to establish a limited number of special Schools. Whatever the present feeling of the various Institutions may be, however jealous they may be of one another, this step will necessarily be taken at no distant date. The public will demand it, as the only means of securing efficient teaching. The development of a suitable course of preliminary studies must be a matter of experiment—it must therefore be in the hands of an independent body of competent teachers: of a School free from interference and independent of external control. If University privileges are to be attached to the Schools, they must be of a certain importance. I imagine that at most three such Schools are required and can be allowed in London. It is most unfortunate that a beginning was not made at South Kensington.

My own personal experience—far from being of the antediluvian order painted by Dr. Wade—enables me to speak with some slight feeling on a proposition such as I advance above. When Prof. Ayrton and I were appointed in 1879 by the City and Guilds of London Institute for the Advancement of Technical Education to start classes in temporary quarters at the Cowper Street Schools, Finsbury, I found plans already drawn for the erection of a separate chemical laboratory on an adjoining site. I at once urged that these should be set aside and that a more comprehensive scheme should be developed, in order that students might receive the general training required to fit them for industrial posts. Plans were elaborated by us with the assistance of Mr. E. C. Robins, an architect and a member of the governing body; later on, in conjunction with Prof. Perry and Mr. Magnus (now Sir Philip Magnus), we drew up the scheme under which the Finsbury Technical College has been worked practically up to the present day. The passing of a simple examination was made a condition of entrance, from the beginning.

We made it a fundamental condition that there should be no external control through examinations, feeling as we did that it would be impossible to develop suitable courses of instruction if the College were hampered by the necessity of following instructions laid down without any reference to the particular work to be accomplished. The Finsbury College has been a remarkable success; the elimination of external examinations has in no way had the detrimental effect pictured by Dr. Wade (p. 639)—on the contrary. Unfortunately, all the Polytechnics which came into existence subsequently elected to worship at the examination shrine—in most cases their progress has been most seriously hampered by this circumstance. At the close of the Inaugural Lecture which Prof. Ayrton delivered at Finsbury, on November 1, 1879, after referring to the wonderful development of the Japanese during the previous ten years, he pointed out that what the City Companies proposed to do was to give workmen that education which will enable them to commence doing what George Stephenson, half a century ago, urged on them: "Learn for yourselves, think for yourselves, make yourselves masters of principles, persevere, be industrious and then there will be no fear for you."

The keynote of the work at Finsbury was struck in this passage.

When in 1885 we passed to what is now the Central Technical College, together with our colleagues we elaborated a scheme which was dominated by this same policy—again we were uncontrolled by external examinations. The success which has attended the College—the fact that it now ranks as the premier Engineering College in the country—is proof that such a system works well in practice. In point of fact, it would not have been possible, we believe, to achieve success under any other less elastic system—the constant modification and improvement of the courses which time has shown to be possible and desirable could not otherwise have been effected. The purpose with which students work would have been altogether different: instead of concentrating their attention on their work and acting under the advice of their teachers, they would have constantly had in mind the possible requirements of the examiners and the nature of the Chinese puzzles they would be called upon to answer. Only those who have worked untrammelled by the cast-iron conditions of a rigid system of external examinations are aware of the terrible limitations which such a system imposes upon both teacher and taught.

In both schools, class examinations have always been held. Of late years, we have had the opportunity at Kensington of testing the effect of holding the examinations at the conclusion of the first year's course in conjunction with external examiners appointed by the University of London and of counting the examinations as the Intermediate examinations for the University degree. The examinations, however, have been strictly on the courses and the practical work done during the whole period of study has been taken into account, students being required to have done this as well as the written work satisfactorily. The effect has been altogether good—whereas formerly students would pay little attention to a subject which did not happen appear in the University syllabus and were liable to ne their work while preparing to solve examiners' riddles, now realise that it pays to give serious attention both to lect and to laboratory work.

The teaching staff at the Royal College of Science, the R School of Mines and the Central Technical College considered the matter together and are unanimous in thin that the method now applied to the Intermediate is the o proper method to be applied in future to the degree examinati (the B.Sc.).

The report has been most sedulously propagated, for politica purposes, by Dr. Wade's friends in Convocation that internal students pass the examinations without any effort, far more easily than the external. I know the very reverse to be the case. It is now possible to insist on a high standard of practical work; and it is possible also to penalise the abominable practice of "cooking" results, which seems to be regarded with entire equanimity by most schoolboys. Under the present external system—although only a few fail to pass who are thoroughly well trained and deserve to succeed, through bad luck in meeting with unfamiliar questions or nervousness—many get through who have no right to pass, being merely crammed for the occasion.

The introduction of the internal system is, in my opinion, the one step of importance taken since the reconstitution of the University—and it was forced on the University by the Schools.

In the course of a speech which he delivered last year, as Chairman, at a dinner of the Graduates Association—which has been printed and widely circulated—the present Vice-Chancellor of the University said that the Association "agreed with Lord Derby in distrusting the teacher as the examiner for degree examinations and does not approve the adoption of degree examinations to fit the teaching of a particular college or Professor." Such a libellous aspersion of the teacher can only be met with the contempt it deserves—but the statement embodies popular doctrine and until teachers are held to be above such suspicion there can be little improvement of their position. The members of the Association who are teachers might well consider whether in thus casting doubt on the honesty of their class, the Chairman is rendering them a service—whether after all they are not catspaws in an agitation which has but commercial ends in view. The narrowness of liberal opinion is too well known to require elucidation and the general tendency to jump at conclusions is well known: but before giving vent to such utterance, the Vice-Chancellor might well have paused to consider whether he and his friends, Lord Derby included, have been in the possession of the knowledge necessary to the formation of a valid opinion. Dr. Wade has described the teaching of my early days as "absolutely destructive of the scientific spirit"—as I had the privilege of numbering the Vice-Chancellor among my pupils, it may be that I am in part responsible for his lack of scientific acumen. But I cannot help thinking that the experience he has had since coming into office and the more intimate knowledge he has gained of the University under somewhat modernised conditions—far removed though these may be from what is desirable—will have convinced him that his dictum is now not of general application, even if he be not yet prepared to admit that it does not apply at all to true University teaching.

In the case of special schools such as I advocate, the teaching should be entirely under the control of the School, including the examinations on the course held in conjunction with qualified external examiners appointed by the University—whose part, however, should be that of sympathetic advisers rather than that of fault-finding critics. The condition of entry should also be determined by the School alone. It is to be hoped that, at no distant date, examinations such as the London Matriculation will come to an end, as being wholly bad in their influence on the schools from which candidates are drawn: owing to the failure of the University to lay down proper conditions and the lack of competent examiners, there is no real standard of excellence but only one of difficulty.

The matriculation examination may be considered to be of value from two points of view—either as affording proof that the person who passes has received a sound education at school; or as proof of fitness to enter on a course of University study. As at present conducted, it subserves neither purpose properly. It is well known that the requirements are not such as can be directly met by schools and that it is necessary to prepare candidates specially for the ordeal, a thoroughly demoralising proceeding. Moreover, those who have passed the examination, judging from my own experience, are in no way specially fitted to proceed to higher studies. During several years past I have each year had the opportunity of comparing the work done by a considerable number of students who have passed the London Matriculation with that done by at least an equal number who have not submitted themselves to this ordeal: although a distinct difference has been noticeable between the two classes—inasmuch as the former have been more assiduous workers, less anxious to waste their time, being drilled in learning lessons—the one class has not been in any way better prepared than the other to enter upon technical studies. The work done in preparation for the University examination has been in no way of special advantage to the students and has not had the effect of rendering them more intelligent: both classes have been equally incapable of using their own language effectively in writing accounts of their work, equally untrained in the use of books, equally lacking in manipulative skill. Indeed, the non-matriculated students, on the whole, have had freer minds and from this point of view have been better students. The impression I have gained is that the matriculation is of value only as a proof of ability to pass an examination of a particular type—of the literary type; in fact, the chief tendency of the examination appears to be to bring about the selection of a bookish type of student. I am persuaded that for all practical purposes a properly conducted College entrance examination is both far superior to the matriculation and free from its unfairness—for many are denied access to the University degrees by failure at matriculation who are quite able to follow University courses of instruction with profit, improving vastly as they gain in experience. It is perfectly easy, in a college entrance examination, to judge which of the candidates are likely to be able to follow the courses; in the few uncertain cases, no doubt remains at the end of the first or second term of instruction and incapables are then easily weeded out.

But the whole subject is full of difficulty. At present we are but moving in a vicious circle. The work done in the schools is unsatisfactory as a preparation, in laying a suitable foundation, for the work to be done at the University; the Universities, however, exercise no proper influence on the schools, owing to the academic unpractical character of their entrance examinations. The two centres of activity need to be co-ordinated and to be brought into effective co-operation. The only way in which it appears probable that we may succeed in introducing the desired reforms is by linking up the secondary schools directly with the University schools, by leaving these latter to determine the conditions under which entry to their courses shall be accorded to scholars from secondary schools. But it will be desirable, as far as possible, to dispense with entrance examinations and to exact evidence of training instead. The system in vogue in the Universities of the Middle-West in the United States of America appears to be the one most deserving of trial. This involves the inspection of the secondary schools by *competent* persons from the University schools and the admission forthwith at the University of pupils from schools duly accredited as providing satisfactory instruction. If during a series of years the pupils from a particular school prove to be unsatisfactory students, the school is struck off the list. A system of this kind would make it possible to bring about the necessary changes in our school system within a very few years—if they entered into the work in the right spirit, University teachers would be able to give advice and assistance to the teachers in the schools which would make it easy for them to improve their teaching. A new spirit of co-operation would be introduced which could not fail to have far-reaching consequences. No headquarters machinery will effect the object I have in view.

Dr. Wade has spoken of the time devoted to preliminary medical studies, especially chemistry—he says, the work cannot be done in less time than is devoted to it at present and more it is impossible to give. The question is one for the future to decide. In my opinion—and I speak from considerable experience—it is undesirable to keep boys and girls at school much beyond sixteen years of age, certainly not beyond seventeen; after this age, they lapse into unsystematic if not irregular habits and are subjected to a discipline unsuited to their years. All further education should be carried on at a place of higher education, under more elastic conditions than school affords and more in sight of the world; under conditions likely to develop independence of character and individuality. On the other hand, it is undesirable, as a rule, that a student should take up serious clinical work under hospital conditions before he is one- or two-and-twenty years of age—the strain is too severe for younger men and the necessary maturity of judgment is rarely developed at an earlier age. From sixteen or seventeen at latest to one- or two-and-twenty should be a period of sufficient length, under proper conditions, for the mastery of the various subjects comprised in the curriculum, short of the purely technical stage. More time could well be found for chemistry than is now given to the subject and as the medical man is, in large measure, a practising chemist, it will come to be recognised, I believe, that he must acquire a sound working knowledge of the subject. Let me add that I would make literary training an important element in the curriculum

As to the teachers—Dr. Wade contends that chemistry must be in the hands of chemists. I agree. But the chemists must be physiologists. The chemistry to be taught will not be mere dry-bones chemistry—anatomical chemistry—but functional chemistry, physiological chemistry in the true sense of the term. Few among our present race of chemists are physiologists even in their own domain; they are mostly mere anatomists. It will be necessary to educate a new type of teacher for the purposes of the medical schools—one who is in full sympathy with medical aims, able to appreciate the character of the problems with which he is faced—a physiological chemist, in fact; it will be necessary, on the other hand, to have physiology taught by chemical physiologists, men who have the same appreciation of chemistry that chemists will have of physiology. The one will have a mastery of the technique of chemistry, the other of the technique of physiology—both sympathising with each other's aims and objects more than either does at present.

As to the state of knowledge of students entering the medical schools, I am quite at one with Dr. Wade that for some time to come it will be necessary to deal with the scientific subjects almost *ab initio*. But I am not inclined to adopt his *laissez-faire* policy as the policy of the future. I hold that it is the duty of the Universities to take the schools in hand without delay and force a sound policy on them. Of what use are Universities if they cannot control the course of higher education—if they do not act as advisers of the public—if they do not promote the spread of new knowledge? The medical schools are now practically all under the control of the Universities. Nothing would be easier than for the Universities to say that after a certain date no one should enter a medical school who could not give evidence of having received sound training previously, during at least three years, in English and the elements of scientific method as applied both to the physical sciences and to biology. Assume that at first many were rejected—parents would be so angry that they would bring pressure to bear on the schools to reform their ways. Some action is needed at the moment which will bring the schools into line with the times—we may be sure that the majority will not change their ways except under compulsion.

If the student be ignorant of scientific method on leaving school, he has not merely wasted precious years: what is far worse is that he has not been disciplined as an observer and experimentalist, as a logical thinker and worker; his mental faculties will have been stunted rather than developed. Unless the art and habit of inquiry be developed in the youthful mind from the earliest days onwards, atrophy of the faculties inevitably sets in, a state of mental inertia being engendered from which it is very difficult to escape. The present system both at school and college is one from which the student receives the minimum of benefit—for the most part the training is not such as to develop scientific habits of mind.

We can apply our knowledge to secure the improvement of appliances—hence the marvellous advance of our civilisation during the past few decades; we can apply it to the study of agricultural problems—to the improvement of plants and brute animals; seemingly, however, we cannot apply it to ourselves. The reason is plain. As Mr. Francis Galton tells us in his *Inquiries into Human Faculty*:

> The vast majority of persons of our race have a natural tendency to shrink from the responsibility of thinking and standing alone; they exalt the *vox populi*, even when they know it to be the utterance of a mob of nobodies, into the *vox Dei* and they are willing slaves to tradition, authority and custom. The intellectual deficiencies corresponding to these moral flaws are shown by the rareness of free and original thought as compared with the frequency and readiness with which men accept the opinions of those in authority as binding on their judgment. I shall endeavour to prove that the slavish aptitudes in man are a direct consequence of his gregarious nature, which itself is a result of the conditions both of his primeval barbarism and of the forms of his subsequent civilisation. My argument will be, that gregarious brute animals possess a want of self-reliance in a marked degree; that the conditions of the lives of these animals have made a want of self-reliance a necessity to them and that by the law of natural selection the gregarious instincts and their accompanying slavish aptitudes have gradually become evolved. Then I shall argue that our remote ancestors have lived under parallel conditions and that other causes peculiar to human society have acted up to the present day in the same direction and that we have inherited the gregarious instincts and slavish aptitudes which have been needed under past circumstances, although in our advancing civilisation they are becoming of more harm than good to our race.

If science is to be of any value to us, it should enable us to bring influences to bear to counteract the innate peculiarities which tend to diminish human efficiency. At present, education, as a rule, has an effect opposite to that which we desire to produce.

My proposals, it will be obvious, are far reaching. They involve, in London, the reorganisation of the University and the recognition of its Schools as dominant factors. All who are in the inner circle and who understand the working of the machine —or rather its failure to work—are aware that it comprises incompatible elements and interests: the recognised Schools, the evening schools or Polytechnics, the coaches and their following —the so-called external students. Our plain duty now is to reconstitute it as an effective organisation in which teaching can take place under conditions of maximum efficiency.

The situation is clearly foreshadowed in the following luminous lines:

"'Tis a pitiful tale," said the Bellman, whose face
Had grown longer at every word:
"But, now that you've stated the whole of your case,
More debate would be simply absurd.

"The rest of my speech" (he explained to his men)
"You shall hear when I've leisure to speak it.
But the Snark is at hand, let me tell you again!
'Tis your glorious duty to seek it!

"To seek it with thimbles, to seek it with care;
To pursue it with forks and hope;
To threaten its life with a railway share;
To charm it with smiles and soap!

"*For the Snark's a peculiar creature, that won't*
Be caught in a commonplace way.
Do all that you know and try all that you don't.
Not a chance must be wasted to-day!

"For England expects—I forbear to proceed:
'Tis a maxim tremendous but trite:
And you'd best be unpacking the things that you need
To rig yourselves out for the fight."

THE BIO-CHEMISTRY OF ANIMALS AND PLANTS

A COMPARATIVE STUDY.—I

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CHEMISTRY, at one time intimately connected with biology, drifted away from this science during the past century, mainly owing to the apparent exhaustion of its methods in their useful application to biological problems. Meanwhile the edifice of chemistry has been perfected to such a degree that chemists are again able to attack biological questions with the help of new experimental methods. In consequence it is being more and more recognised that the sharp separation of animal and vegetable biology has only been an artificial one and does not really exist. Formerly it was held that the plant alone possessed the power of building up organic substances, *i.e.* of synthesis. The animal body, it was thought, had mainly the function of breaking down the substances supplied to it by the plant. The first synthesis taking place in the animal body was demonstrated by the classical work of Wöhler in 1824, when he showed that benzoic acid in its passage through the body was linked up to glycine and excreted as hippuric acid. Many similar instances of synthetical processes occurring in the animal body have since been found (to mention only the latest one, *i.e.* the synthesis of proteins from amino acids), and although no doubt the synthetical power of the animal organism is less than that of the plant, we know now many biological processes which are common to both.

The purpose of the following pages is to discuss in outline some of the progress made in this "Grenzgebiet" (borderland) of bio-chemistry.

THE NITROGENOUS CYCLE

If we consider first the nitrogenous substances which play such an important rôle in the animal organism, it is evident that they occur there in far larger proportion than in the plant, whereas the latter contains a preponderance of carbohydrates and other substances which are free from nitrogen. Here we are at the outset confronted with a fundamental difference between animals and plants, which seems to find an explanation, if we consider that the nitrogen supply of plants (apart from atmospheric nitrogen) is not at all abundant, whilst on the other hand in the carbonic acid of the air, which by the aid of the energy of sunlight they are able to transform into carbohydrates, plants possess a seemingly inexhaustible supply of carbon. Nitrogen-free carbon compounds accordingly perform functions in the plants for which there is no analogy in the animal organism, *e.g.* cellulose, in the cell membrane. It can, however, be easily demonstrated that a sufficient supply of nitrogen is one of the essential factors for plant life, and that the protoplasm of the plant contains proteins as certainly as does the protoplasm of an animal; further, that the properties and behaviour of the vegetable proteins are very nearly allied to those of animal origin.

It is a fascinating problem, which the comparative study of vegetable and animal biology has helped to solve, to investigate the great cycle of nitrogen in Nature. Here again we meet with another fundamentally important difference of animal and vegetable metabolism. The animal organism relies as the only source for its protein anabolism either on protein itself or on its direct cleavage products. It is unable to form protein material from inorganic compounds, nor does the animal cell possess the property of utilising other organic nitrogenous compounds, which have no direct relation to proteins. The animal organism, in short, depends entirely for its source of nitrogen on the vegetable world.

The raw products available to the plant for the synthesis of proteins are, mainly, the free nitrogen of the atmosphere, ammonia salts, nitrates and nitrites in the soil and organic nitrogenous substances of various kinds which are furnished by the decomposition and decay of animals and plants, such as amides, amines, amino acids, and amino salts of organic acids.

In the protein synthesis of the plant from these materials a most important rôle is played by bacteria, those micro-organisms which take an intermediate place between animals and plants. The recognition of their importance is entirely the outcome of modern methods of investigation. This knowledge is of recent origin, and a short consideration of the main changes produced in nature by bacterial activity is essential in order to understand the nitrogenous cycle.

Nitrification.—As a final product of decay of plants or animals brought about by micro-organisms, the nitrogenous substances furnish mainly ammonia. This is transformed in the soil into nitric acid and nitrates, and enormous deposits of saltpetre have been formed in this way on the earth's surface under certain conditions. It was originally pointed out by Sir Humphry Davy that saltpetre is formed by the help of the oxygen of the air from the ammonia present in the soil, but the fact that this saltpetre formation, now usually called nitrification, is due to a biological process, carried out by the activity of microbes, has only been demonstrated in recent times. It was not until 1890 that Winogradsky succeeded in producing pure cultures of these organisms. This achievement offered great difficulties until it was found that these organisms grow best in a completely inorganic medium. They are able to obtain all their necessary carbon and nitrogen from ammonium carbonate. This nitrification process is the work of several kinds of microbes, one class called "nitrosomonas," oxidising ammonia to nitrites, and the other class, called "nitrobacter," which oxidise nitrites to nitrates. It has been shown that a large amount of organic nitrogen is transformed into nitrates in the soil and thus it is made available for the building up of the protein material of vegetable protoplasm. This is used as food for animals, and the largest amount of the protein-nitrogen of food is excreted by them in the urine, as urea or uric acid, to be transformed, also by bacterial activity, into ammonia and finally in the soil into nitrates.

Denitrification.—Whilst the nitrogenous cycle would thus appear to be a relatively simple one, another very old observation seems to break its continuity. Long ago Davy discovered that free nitrogen is formed in large quantities during the decomposition of organic substances. Towards the end of last century it was finally established that we have to deal here also with the work of microbes, which, however, work only in the absence of oxygen. This process is called "denitrification," and the organisms which are the cause of it reduce nitrates to nitrites and ammonia, and finally to free nitrogen. So active are some of them in pure cultures that the process of nitrogen evolution resembles an alcoholic fermentation and has been aptly termed "nitrate fermentation." There cannot be the slightest doubt that by this process there is continually set free on the surface of the earth an enormous quantity of nitrogen which is apparently lost to organic life.

N-Fixation. — A solution of this apparent contradiction, although already foreseen by Berthelot, has finally been furnished and proved by the exact experimental work of Winogradsky. He succeeded in 1893 in isolating a bacillus, called by him *Clostridium Pasteurianum*, from the soil which is able to utilise directly the nitrogen of the air for building up its protein substance. A large number of similar microbes, mainly anærobes, have subsequently been isolated by other workers. That the absorption of nitrogen by these organisms takes place in large quantities is proved by experiments on trial fields, and it has been calculated that about 30 kg. nitrogen per acre are made available yearly.

This is, however, not the only way by which the atmospheric nitrogen is utilised by organic life.[1] It has long been accepted amongst farmers as a well-established fact that wheat grows better on fields on which previously leguminous plants such as clover had been grown. Biologists took no notice of this result of practical experience until quite recently. The whole process has now been completely cleared up, the work beginning with the careful investigations of Hellriegel in 1886. He was the first to establish accurately the fact that leguminous plants possess the property of absorbing atmospheric nitrogen, and he showed the connection of this property with the formation of root nodules and the presence of bacteria. To Beijerinck (1886) belongs the merit of having succeeded in isolating these bacteria in pure cultures and showing that a bacillus, called by him *B. radicicola*, enables the plant by a symbiotic process to absorb elementary nitrogen from the atmosphere and to make use of it for its growth. These observations have been extended by Nobbe, Hiltner, Frank, Moore, and others[1] and showed that many strains of this bacillus exist and that a favourable influence on artificial infection is only noticed when cultures obtained from nearly related families are used, *e.g.* bacteria from peas will produce nodule formation in peas, but not in robinia roots. It is also interesting to note that the Japanese *Soja hispida* very often does not grow nodules in European soil, but produces them when inoculated with Japanese soil. Nothing is known so far about the initial products formed by the bacteria from nitrogen, but it is assumed that proteins are finally produced which are made use of by the plant.

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[1] An allusion might here be made to the successful modern methods of nitrogen fixation from the air by electro-chemical means (calcium-cyan-amide, calcium nitrate). As it has been stated that the saltpetre fields of Chili will be exhausted within the next fifty years, such considerations are of practical importance.

Still another stage in the nitrogen cycle must be mentioned, since it helps us to understand the conditions of plant and animal life in sea-water. By the solvent agency of rain-water, soluble nitrogenous substances such as nitrates are drained out of the soil and finally carried by rivers into the sea. An enormous amount of nitrogen (Brandt calculates it at 40,000,000 gr. per annum) is thus lost to the dry land, and this is largely in excess of that nitrogen removed from the sea in the same period in the form of food fishes and other animals. The question arises, how these large quantities of nitrogen are again returned to circulation, and in this direction the discovery made by Baur in 1902 is of the greatest importance. He demonstrated the general occurrence of denitrifying bacteria in sea-water and mud. These continually throw again into circulation the nitrogen carried into the sea by the rivers, or which has accumulated there owing to the decay of plant or fish life. The discovery of the denitrifying bacteria in sea-water also helps us to solve another apparent contradiction. On the dry land the tropical and subtropical regions are more thickly populated by plant and animal life than the regions nearer the poles, whereas in the sea just the reverse is the case. In accordance with this the nitrogen content of southern warmer sea areas is smaller than that of northern colder ones. Now it has been shown that the development of the denitrifying bacteria stands in close relationship to temperature. Whilst at the temperature of the tropical seas (25–30°) the nitrogen evolution is most marked, the denitrifying bacteria are condemned to inactivity at the low temperatures of 4–15° of the northern seas, and thus the nitrogenous materials are left available for plant and subsequently for fish life.[1]

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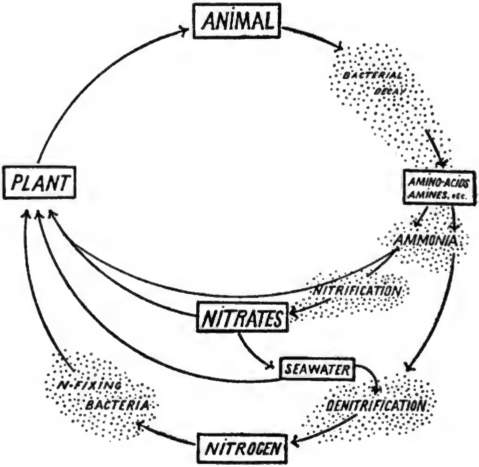
[1] For a complete list of the literature from Pliny to 1901, see E. Jacobitz, *Centralb. f. Bact.* II. vol. vii. 1901, 783.

We are now able to finish the picture of the nitrogen cycle in Nature, and the following schematic drawing is left to speak for itself:



THE SYNTHESIS OF PROTEIN IN PLANTS

Moulds.—The statements that some fungi (*Aspergillus* and *Penicillium* varieties) are able to fix atmospheric nitrogen like certain bacteria have so far not been sufficiently established. Moulds and yeasts, however, are able to satisfy their nitrogen want by making use of ammonia salts and nitrates. For yeasts, nitrates are less suitable than for moulds. It has further been shown that the latter synthesise their protein material still better if simple amino acids are offered to them. For one of the commonest moulds, *Aspergillus*, it was demonstrated by

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[1] For a detailed account of these and similar problems, see J. Johnstone, SCIENCE PROGRESS, vol. ii. 1907, 191.

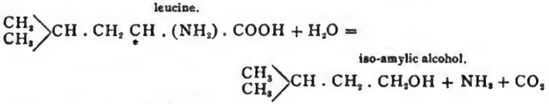
Czapek and by Emmerling that the food value of the α-amino acids is superior to that of all other nitrogenous substances. Abderhalden and Rona proved subsequently that this mould builds up its protein in the same way, if grown on potassium nitrate, glycine, or glutaminic acid, and that the protein thus formed in the living organism remains constant in composition, *i.e.* furnishes identical cleavage products on hydrolysis. As an explanation for this interesting observation we must assume that the *Aspergillus* starts with the amino group in the building up of its protein.

Yeasts.—A subject of considerable biological interest and at the same time of practical value is the study of the nitrogenous metabolism of yeast. To mention the name of "fusel oil" in this connection seems to be going away from the subject, but it is not really so, for the intimate association of protein formation and "fusel oil" has been made clear by the researches of F. Ehrlich, and these deserve to be referred to in some detail.

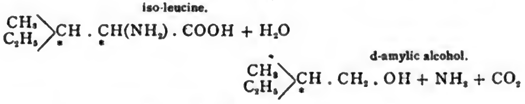
Of the various by-products of the alcoholic fermentation of carbohydrates by yeast (such as glycerin, succinic acid, ethers, aldehydes, etc.), fusel oil is the least desirable from the distiller's point of view. It was discovered by Scheele in 1785, and was shown by Pasteur to consist of higher alcohols and especially two amylic alcohols. Its smell and taste are disagreeable, and the deleterious action of certain raw spirits has, although probably without justification, been ascribed to it. The separation of fusel oil from ordinary ethyl alcohol was one of the difficulties of alcohol manufacture, which was finally solved by the perfection of fractional distillation. With the introduction of better methods, especially the use of pure yeast cultures, a distinct falling off in the quantity of fusel oil formed took place, whilst on the other hand the demand for this product for industrial processes rose to such an extent as to produce a scarcity in the world's markets. Amylic alcohol in the form of its ethers is now in great demand for the manufacture of fruit essences, celluloid, and smokeless powders. While investigating the conditions of fusel-oil formation, the view found most general acceptance that its origin was due to a bacterial decomposition of sugar. The fact, however, that the alcohols of fusel oil possess a branched carbon-chain, and that the addition of the so-called "fusel bacteria" did not increase the output of fusel oil in normal fermentation, soon disposed of this idea.

To F. Ehrlich belongs the credit of having discovered the exact conditions for the production of fusel oil, and its close connection with protein synthesis from amino acids in the growing yeast cell. The application of the results of modern researches on protein constitution, and the amino acids produced by its cleavage, led him to this solution. He discovered iso-leucine in molasses as well as in yeast, and as a constant proteolytic cleavage product of other proteins (fibrin, caseinogen), and this, together with the general occurrence of amino acids in plant juices and the similarity in constitution of leucine to iso-amylic alcohol, led him to the view that amylic alcohol and its homologues are produced from amino acids by the agency of yeast itself. The conclusive proof for the correctness of this view was the discovery that the fermentation of these amino acids by means of pure yeast cultures occurs in the presence of sugar. In this way Ehrlich succeeded in obtaining iso-butyl alcohol from valine, iso-amylic alcohol from leucine, and d-amylic alcohol, the only optically active constituent of fusel oil, from iso-leucine in quantities corresponding to the amount of amino acid which he had added. Whilst the highest percentage of fusel oil of raw spirit was formerly 0·5 per cent., it is now possible by these means to increase it ten to twelve times.

The formation of the higher alcohols from the amino acids admits of a very simple chemical explanation. With the addition of water a simultaneous splitting off of CO_2 and NH_3 takes place, as expressed by the following formulæ[1]:



$$\left.\begin{matrix}CH_3\\CH_3\end{matrix}\right\rangle CH\,.\,CH_2\,\underset{\bullet}{C}H\,.\,(NH_2)\,.\,COOH + H_2O = \left.\begin{matrix}CH_3\\CH_3\end{matrix}\right\rangle CH\,.\,CH_2\,.\,CH_2OH + NH_3 + CO_2$$



$$\left.\begin{matrix}CH_3\\C_2H_5\end{matrix}\right\rangle \underset{\bullet}{C}H\,.\,\underset{\bullet}{C}H(NH_2)\,.\,COOH + H_2O \quad \left.\begin{matrix}CH_3\\C_2H_5\end{matrix}\right\rangle \underset{\bullet}{C}H\,.\,CH_2\,.\,OH + NH_3 + CO_2$$

During the growth of the yeast cell these reactions probably take place by means of an enzymatic action, and the ammonia is directly used up for the formation of protein. The fusel-oil formation depends not only on the amount of amino acids, but also on the kind and quantity of other nitrogenous substances present. In the presence of easily assimilated nitrogen, such as asparagine or ammonium salts, practically no fusel oil is formed. Ehrlich has also applied this process for the preparation of optically active amino acids from the racemic inactive compounds, one component only being transformed into the corresponding alcohol. But not only is yeast able to use leucine and iso-leucine as a source of nitrogen for its protein formation, but also all the other *a*-amino acids, *e.g.* tyrosine is converted into p-oxy-phenyl-ethyl alcohol, and phenyl-alanine furnishes phenyl-ethyl alcohol. The formation of this latter substance, which represents the largest bulk of the essential oil of roses, opens a new outlook for another branch of plant physiology, the formation of essential oils and their connection with proteins.

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[1] $\underset{\bullet}{C}$ = asymmetrical carbon atom.

Carnivorous Plants.—Of great interest is the existence of plants which secrete products analogous to the digestive juices of animals, and which are able to digest insects or proteins. This great group of carnivorous plants comprises *Drosera*, *Pinguicula*, and *Utricula* varieties, etc. The various kinds of *Nepenthes* act on a larger scale, catching and digesting insects by means of the liquid in their pitchers. It is still doubtful whether the action of these enzymes corresponds to that of pepsin or trypsin, although some recent preliminary experiments by Abderhalden and Terunchi make it probable that it is not of a trypsin nature. They found that the dipeptide glycyl-l-tyrosine is a very convenient substance to distinguish between pepsin and trypsin, as it is not attacked by the former, but easily split into its components by the latter. The juice of *Nepenthes* has no appreciable action on this dipeptide. Recently Vines has succeeded in showing that an enzyme of the nature of erepsin occurs largely in plants and also to some extent in *Nepenthes* pitchers. This enzyme was originally discovered by Cohnheim in the intestinal mucous membrane, and it was shown by Vernon to be generally present in all animal tissues. It has no action on proteins as such, but splits peptones, albumoses, and polypeptides into amino acids. One would expect that the carnivorous plants would be able to use amino acids themselves or higher cleavage products for their protein synthesis. There has been very little work done on the metabolism of carnivorous plants, and this point has not been investigated. That plant organisms exist which produce their protein from the higher cleavage products alone has, however, been made clear by the researches of Beijerinck, who proved that the alga living symbiotically with *Physcia parietina* requires peptones (*i.e.* albumoses) for its normal growth.

Higher Plants.—Relatively little is yet known about the protein synthesis in plants containing chlorophyll. The study of the processes occurring during germination has attracted many investigators, and has furnished most useful results. The ripe seeds nearly always contain a large store of protein. As soon as germination begins great changes take place in cells. The proteins are decomposed by the action of proteolytic ferments, the existence of which, during germination, has been definitely proved. By the action of these ferments the higher cleavage products first obtained from the proteins are finally converted into simple amino acids, which are partly at least made use of at once by the growing plant. We may compare the process of germination with that occurring during digestion in the animal body. In both cases the complex food protein is first decomposed into simpler cleavage products, and it is from these that the organism reconstructs the protein matter of its protoplasm. A long series of amino acids, leucine, tyrosine, aspartic acid, glutaminic acid, arginine, lysine, histidine, etc., have been isolated from germinating seeds. A peculiar occurrence is the formation of asparagine and sometimes of glutamine, substances which have not been observed in any artificial protein hydrolysis. By allowing seeds to germinate in the dark, *i.e.* under normal conditions, large amounts of these two substances may be produced. The significance of asparagine formation is not yet fully understood. Pfeffer has shown that the increase of the asparagine is coincident with the decrease of carbohydrate formation in the absence of light, which stands in close relationship to the protein synthesis, the absence of which entails an accumulation of amino acids. It is possible that asparagine represents a transition stage in the formation of other nitrogenous substances, or perhaps that it is connected with carbohydrate and fat formation. This view is confirmed by certain observations made upon tyrosine. This amino acid is produced in large amounts during the initial stages of the germination. By the action of a ferment, which can easily be localised, it is, however, very quickly converted into a nitrogen-free substance—homogentisinic acid. This same substance, by the way, is formed from tyrosine in the human body under certain abnormal conditions and excreted in the urine, giving rise to so-called alkaptonuria.

After the exhaustion of the nitrogen supply from the seed, the plant depends for its nitrogenous foods on the nitrates and ammonia salts of the soil. Those plant organs seem to be predestined to carry out the protein synthesis in the adult plant, in which carbohydrate formation is also most vigorous; and it was pointed out by Sachs in 1865 that the leaves perform the largest share of this work. Very little definite knowledge exists with regard to the actual processes. It is generally accepted now that the first substances formed are amino acids, and that by the linking of these together into complex chains the proteins are ultimately produced. Light plays a most important part in the protein formation in leaves. Whilst leaves are unable to make use of free nitrogen, several observations confirm the view that small amounts of ammonia are absorbed. The protein synthesis in leguminous plants, which takes place by the help of bacteria, has already been discussed (p. 679).

PROTEIN SYNTHESIS IN THE ANIMAL ORGANISM

Since Loewi's experiments, which showed that in animals weight, health, and nitrogenous equilibrium can be maintained for a considerable time by feeding them on the crystalline cleavage products of protein hydrolysis, the old view that the albumoses and peptones are absorbed as such has been steadily losing ground. The belief is now general that the largest part of the ingested protein undergoes cleavage into its fundamental amino acids, and that the body exerts a selective power in building up its various proteins from these comparatively simple materials. Evidence is accumulating which confirms this view, and of the many researches in this direction, those of Abderhalden and his collaborators should be specially mentioned.[1]

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[1] This question has been fully discussed by F. G. Hopkins, SCIENCE PROGRESS, vol. i. 1906, 159, and by E. P. Cathcart, *ibid.* vol. ii. 1907, 76.

The Vegetable Proteins

The preponderance of carbohydrates in plants explains the fact, shown in the history of plant physiology, that the general occurrence of nitrogen in plants has been recognised relatively late, and that the presence of proteins especially has been considered as an exceptional occurrence.

History.—From an historical point of view it is interesting to note that the earliest known vegetable protein was wheat gluten; this was isolated by Beccari in the eighteenth century. Berzelius examined it at the beginning of last century and called it "vegetable glue" or "vegetable casein" on account of its similarity to the corresponding animal substances. Braconnot isolated about the same time the proteins of peas and beans, which he called "legumin." Gay-Lussac subjected vegetable proteins to elementary analysis, and was the first to point out the general occurrence of proteins in seeds. But Liebig and his pupils were the real founders of the system which led to our modern knowledge of protein chemistry. He distinguished between plant albumin (coagulated by heat, not precipitated by acids), plant casein (not coagulated by heat, not precipitated by acids), and plant fibrin. The view also originated from his laboratory that elementary analyses of proteins teach us very little about the nature of these substances and that more knowledge is obtained by the investigation of their hydrolytic cleavage products. The classical work of Ritthausen, published in 1872, was the outcome of the application of these methods to vegetable proteins. Ritthausen's work still remains of importance, although his methods have been superseded by the introduction of neutral salts for the purpose of isolation and separation of proteins. The names of Hoppe-Seyler, Weyl, Schmiedeberg, must be mentioned in this connection. It was mainly Kühne's pupil, Chittenden, and later Osborne, two American workers who applied the method of fractional salt precipitation to vegetable proteins. This method is still a valuable one, and it is to be hoped that together with the latest processes for the isolation of hydrolytic cleavage products, which we owe to the genius of E. Fischer, we shall be able in the near future to form clearer ideas of the constitution of proteins.

Occurrence and Properties.—With regard to most of the proteins of leaves and roots we are ignorant of the state in which they are present in the cell sap and the cell protoplasm, and indeed in most cases the proteins of the fully grown plant have received but little attention. The best-known vegetable proteins are those which occur stored up in the seeds as "reserve" food for the growing organism, and they show many analogies with the corresponding animal proteins. As a rule they resemble in their chemical and physical behaviour the animal globulins, *i.e.* they are insoluble in water, but soluble in salt solutions and precipitated by dilution or by removal of the salts by dialysis. They crystallise very often inside the cell itself and they were the first crystallised proteins known (Hartig, 1853). Protein crystals are found especially in the endosperm of oily seeds, in the so-called "aleurone" grains (especially of the Para nut, castor-oil seed, etc.). From their solutions they can again be obtained in a crystalline form by relatively easy means. The methods introduced by Hofmeister for the crystallisation of egg albumin have not yet been applied to vegetable proteins. It is a remarkable fact that whilst the vegetable globulins crystallise most easily, the animal globulins have not yet been obtained in crystalline form.

Most of the vegetable proteins, however, like those of the animal body, are characterised by their colloidal nature. Still, numerous transition stages between the colloid and crystalloid condition are also found; thus many vegetable proteins are soluble in alcohol, have lost their property of being coagulated by heat, and have a diminished viscosity. The vegetable proteins examined so far are all lævo-rotatory.

Constitution of the Protein Molecule. Protein Hydrolysis.—Elementary analysis and the study of the physical properties and chemical reactions of the animal and vegetable proteins have led to their classification into more or less well-defined groups. These are subdivided according to purely external characteristics, such as origin, solubility, coagulability, etc. On the basis of such properties we distinguish to-day some forty to fifty natural proteins, and this number will probably increase as the methods of differentiation are improved. A better knowledge of the probable constitution of the protein has, however, resulted from the attempts to study systematically their cleavage products. The means which were made use of to obtain this end were the action of enzymes, of acids and alkalies in varying proportions, of water under increased pressure, of oxidising and reducing agents, etc. Of all these methods two have led to the most constant and useful results—namely, hydrolysis by means of ferments and by dilute mineral acids—and these methods play at present a most important rôle in protein chemistry. Whilst the last method has led to a knowledge of the final cleavage products, the intermediate substances, which still show protein characters, have been made available for further study by the use of enzymes. The well-known stages of enzyme action are the albumoses or proteoses, the peptones and amino acids. Only quite recently E. Fischer has demonstrated an intermediate stage between the peptones and the amino acids by the isolation of the so-called polypeptides, which promise to be of the highest importance for the chemistry and biology of the proteins.

The ideal aim of the chemist would be to separate the complex mixture of cleavage products quantitatively in such a way as to account for the whole of the carbon, nitrogen, and sulphur in the original protein. This idea will, however, probably never be attained on account of the secondary reactions taking place during hydrolysis, such as formation of brown and black pigments, splitting off of CO_2, etc. Even with the best methods at his disposal, E. Fischer has succeeded so far only in separating at the utmost 50 to 70 per cent. of the amino acids present in the cleavage products.

Under these circumstances it is of the greatest value to be able to obtain by a short and reliable procedure at least an approximate knowledge of the nitrogen distribution in the protein molecule, even if this does not allow us to determine quantitatively the single cleavage products. Such a method has been worked out, mainly in Hofmeister's laboratory, by Hausmann, and has been subsequently found trustworthy by Osborne and others.

Hausmann's method is shortly as follows: The whole nitrogen of the protein is estimated by Kjeldahl's method. A weighed amount of the substance is then hydrolysed by means of hydrochloric acid. After complete hydrolysis the cleavage products are separated into three classes, and the nitrogen estimated in each by means of Kjeldahl's method as—

1. Amide-N or ammonia nitrogen. This comprises the nitrogen of that part of the protein molecule which is easily

split off as ammonia, and is determined by distilling off the ammonia with magnesia.

2. Diamino-N. The fluid, free from ammonia, is precipitated by phosphotungstic acid, and the nitrogen present in the precipitate determined. This represents the nitrogen of most of the diamino acids, such as histidine and arginine.

3. Monoamino-N is estimated in the residual fluid after removal of the amide and diamino-N.

Although this method is not absolutely correct, it has nevertheless furnished most valuable information when applied to different animal and vegetable proteins, as is shown in the following table from the analyses of Osborne:

	Total N.	Amide-N.	Diamino-N.	Monoamino-N.
Zein (maize)	16·13	2·97	0·49	12·51
Hordein (barley)	17·21	4·01	0·77	12·04
Gliadin (wheat)	17·66	4·20	0·98	12·41
Glutenin (wheat)	17·49	3·30	2·05	11·95
Globulin (wheat)	18·39	1·42	6·83	9·82
Leucosin (wheat)	16·93	1·16	3·50	11·83
Edestin (hemp)	18·64	1·88	5·91	10·78
Excelsin (Para nut)	18·30	1·48	5·76	10·97
Caseinogen (milk)	15·62	1·61	3·49	10·31

These figures show interesting differences between otherwise similar proteins. New characteristics are given for some protein groups, *e.g.* the alcohol soluble vegetable proteins, which possess a high amide-N and low diamino-N. In Osborne's analyses (not given) of various so-called edestins, great differences of the diamino-N was revealed. The method has also proved useful for the differentiation of albumoses (Pick), and interesting deductions as to the food value of various proteins were drawn from its results (Blum). As 80 to 90 per cent. of the carbon of proteins (according to Kossel) is present in combination with nitrogen, the method is likely to give important clues as to the constitution of different proteins.

Cleavage Products.—The following is a list of the main substances so far met with among the hydrolytic products of proteins; they are classified roughly under the divisions of Hausmann's method, and in each case the constitutional name and discoverer of these substances are given:

Monoamino-N

Glycine (amino-acetic acid, Braconnot 1820).
Alanine (amino-propionic acid, Weyl 1888).
Valine (amino-valerianic acid, Gorup-Besanez 1856).
Leucine (amino-caproic acid, Proust 1818).
Iso-leucine (amino-caproic acid, Ehrlich 1903).

Serine (oxy-amino-propionic acid, Cramer 1865).
Phenylalanine (phenyl-amino-propionic acid, Schulze and Barbieri 1881).
Tyrosine (oxy-phenyl-amino-propionic acid, Liebig 1846).
Tryptophane (indole-amino-propionic acid, Hopkins and Cole 1901).

Aspartic acid (amino-succinic acid, Plisson 1827).
Glutaminic acid (amino-glutaric acid, Ritthausen 1866).

Proline (pyrrolidine carboxylic acid, Fischer 1901).
Oxyproline (oxy-pyrrolidine-carboxylic acid, Fischer 1902).

Diamino-N

Ornithine (diamino-valerianic acid, Jaffe 1877).
Lysine (diamino-caproic acid, Drechsel 1889).
Arginine (amino-guanidine-valerianic acid, Schulze and Steiger 1886).
Histidine (amino-imidazole-propionic acid, Kossel 1896).
Diamino-trioxy-dodecanic acid (Fischer and Abderhalden 1904).
Cystine (diamino-dithio-d-lactic acid, Wollaston 1810).

The proportions in which the various amino acids are obtained from different proteins vary considerably. The quantitative examination of various proteins, by the help of the methods introduced by A. Kossel and E. Fischer, is being carried out at present in many laboratories, and has already furnished most valuable results, *e.g.* albumins are distinguished from globulins by their complete lack of the glycine group, whilst on the other hand gelatin furnishes as much as 17 per cent. of this substance. The latter protein, however, does not yield any tyrosine or tryptophane. The alcohol-soluble vegetable proteins are characterised by their complete lack of glycine and lysine, and are especially rich in glutaminic acid (gliadin of wheat containing 36 per cent.). Some animal proteins, such as the protamines, yield enormously high percentages of arginine (salmine = 84 per cent.). It is worth noting in this connection that in the hydrolysis of all important proteins which play the chief part in animal or vegetable metabolism, all these amino acids occur almost without exception, so that the conclusion must be drawn that none of them can be dispensed with in organic life.

Synthesis.—The study and isolation of the hydrolytic cleavage products have thus been shown to be of the greatest importance. As the same substances are not only formed by the action of acids and alkalies, but also by the agency of the digestive enzymes, they are to be regarded as the true "Bausteine" (building stones), of which the complicated protein molecule is built up. Starting from this idea E. Fischer has been able to build up, by linking together simple amino acids (a process the reverse of hydrolysis), substances which he called polypeptides. These are very similar to the polypeptides which he isolated from digestive mixtures, and even some of the relatively simple ones, such as l-leucyl-triglycyl-l-tyrosine, exhibit many of the properties of the albumoses. The octa-deca-peptide derived from fifteen molecules of glycine and three molecules of leucine, having the high molecular weight of 1213, is a substance which, in its external properties, closely resembles many natural proteins. More than one hundred of these artificial polypeptides have already been synthesised, and we may expect in the near future the announcement of the synthesis of what E. Fischer regards as the simplest protein, namely silk-fibroin, which according to his researches only contains four different amino acids.[1]

Classification of Vegetable Proteins.—The classification of the proteins in general is at present under revision, and can only be a provisional one in view of the rapid progress being made in their chemistry. It is possible that shortly the increased knowledge of the cleavage products and their quantitative relationships will produce an important change in our present classification. With regard to the vegetable proteins, this is all the more desirable, as they can only be fitted in with difficulty into the present system. A complete up-to-date treatise[1] of the vegetable proteins has still to be written, and their nomenclature and classification are at present in a most unsatisfactory and perplexing state. For the purpose of this paper the material to be dealt with has been divided into four main classes, it being recognised, however, that this classification can only be a tentative one, and open to criticism.

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[1] For a complete account of Fischer's work see his book, *Untersuchungen über Aminosäuren, Polypeptide und Proteïne*, 1906; also R. H. Aders Plimmer, SCIENCE PROGRESS, vol. ii. 1907, 88.

The following classes are proposed:

1. Phyto-albumins.
2. Phyto-globulins.
3. Gliadins (alcohol-soluble proteins).
4. Phyto-caseins (phyto-vitellins).[2]

1. The proteins of the first class are the least known of vegetable proteins, the reason for this being that the seeds, which form the main source for the study of plant proteins, contain albumins only in relatively small proportions. Many observations show, however, that they are also present in leaves and the cell-sap of other parts of plants.

The vegetable albumins possess the same characteristics as those of animal origin. They are soluble in water and salted out by ammonium sulphate and other salts. They require a larger amount of salt for their precipitation than the globulins. They may be separated from the latter by dialysis, remaining in solution after the removal of the salts. They have not yet been obtained in a crystalline form, are coagulated by heat, and show all the typical colour reactions of the proteins. They are phosphorus-free.

The best known of the vegetable albumins is a substance called *leucosin*. It occurs in small quantities in grasses, but has been prepared mainly from wheat grains (also rye, barley, and maize), in which seeds it is present to the extent of 0·3—0·4 per cent. For its preparation the seeds are extracted with water or dilute salt solutions, the whole of the dissolved proteins precipitated by saturation with ammonium sulphate, and a solution of the precipitate subjected in dialysis. The globulins become insoluble with the removal of the salt, and from the remaining aqueous solution leucosin may be precipitated in the usual way. It is coagulated at a temperature of 52°; this is lower than the heat-coagulating point of the corresponding animal albumins. It contains 16 per cent. N. and 1·5 per cent. S. and on hydrolysis it furnishes nearly four times as much mono-amino-N as diamino-N.

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[1] Only two exhaustive treatises exist on vegetable proteins: *Die Eiweisskörper der Getreidearten*, etc., Ritthausen, 1872; and *Die Proteide der Getreidearten*, etc., Griessmayer, 1887. The latter is a translation of Chittenden and Osborne's collected older papers.

[2] The name "Glutelin" has recently been proposed by a committee of the American Physiological Society for these substances.

2. *The Phyto-globulins.*—The best-known vegetable proteins belong to this class, and they represent the main reserve proteins of the seeds. Their properties are so much like those of the animal proteins that they have been considered by Chittenden and Osborne—to whom we are mainly indebted for our knowledge about them—as directly analogous to the animal globulins. The ease with which many of them assume a crystalline form, however, distinguishes them from the animal globulins. It is true that lately a doubt has been expressed by Wiman as to their globulin character, as he found 0·4 per cent. phosphorus in legumin, the globulin of peas. But Osborne upholds his view that the purified substances must be considered as phosphorus-free real globulins. Only phosphorus-free proteins ought to be included in this class.

The best-known representative of this class, and one which, on account of its easy preparation, has been most thoroughly examined, is *edestin*. It seemed from their properties and composition that the various crystallised globulins called edestin, and obtained from the seeds of wheat, oat, maize, sunflower, cucumber, cotton, flax, and hemp, represent all one and the same substance. But the analysis by Hausmann's method, carried out by Osborne and Harris, revealed distinct differences in their molecular constitution. Edestin is easily prepared in large quantities from hemp-seed, which contains about 6—8 per cent. edestin. The seeds are first treated with benzene, to remove the oil, then extracted with 5 per cent. salt solution at 60° C., and filtered warm. On cooling, edestin crystallises out, and may be easily recrystallised in the same way. It usually forms well-defined octahedra, but on slow crystallisation prismatic crystals may be obtained. Its insolubility in water distinguishes it from the albumins; it is, however, easily soluble in salt solutions, and gives most of the usual protein tests. It contains 18·5—18·8 per cent. N and 0·8—0·9 per cent. S, and is phosphorus-free. Its heat-coagulation temperature is at about 90°, much higher than that of the animal globulins. Abderhalden has recently examined its cleavage products.

Another very well-crystallised globulin of this class is the protein of the Para nut (*Bertholletia excelsa*), which has been called *excelsin* by Osborne. It occurs in a crystalline form in the aleurone grains in the endosperm of this fruit, and can be easily obtained as hexagonal crystals in a similar way to that described for edestin, which it resembles in character and composition. Its hydrolytic cleavage products have recently been isolated by Osborne and Clapp. A striking feature is the unusually large proportion of arginine found (16 per cent.). A very similar protein has been obtained by Osborne in a crystallised form from oats, and called by him *avenalin*.

The proteins of leguminous plants have been fairly well examined, and must be included in this class. The globulin of beans, which is called *phaseolin* (discovered by Ritthausen), amounts to about 20 per cent. of the seeds, which contain also about 2 per cent. of a second globulin of a greater solubility called *phaselin*. They contain less nitrogen and sulphur than edestin and excelsin. The globulin of peas is called *legumin*. It is not precipitated by sodium chloride or magnesium sulphate on saturation, and gives a rose-red biuret reaction, like peptone. It is also only partially coagulated by heat. The mono-amino-acids of its hydrolytic products have been examined by Abderhalden and Babkin, and these are very similar to those obtained from *conglutin*, the protein isolated by Ritthausen (and subsequently studied by Osborne) from lupins. The name of conglutin had formerly been given to a series of proteins isolated from almonds, peach kernels, walnuts, etc. Osborne and Campbell showed that these proteins differed from conglutin, and accepted the name "amandin" originally given by Proust, for the protein of almonds and peaches. The protein of the hazel nut (*Corylus*) has been called *corylin* by Osborne and Harris. This differs from the globulin of walnuts (*Juglans*), which has been termed *juglansin* by the same observers, in containing more amide-nitrogen, and in being less readily precipitable by ammonium sulphate. For the separation and distinction of these and other vegetable proteins, fractional precipitation by ammonium sulphate (introduced by Hofmeister) and the application of Hausmann's method proved most useful.

3. *The Alcohol-soluble Proteins.*—The substances belonging to this class, for which the general name *gliadin* is proposed, and which possess no direct analogues amongst the animal proteins,[1] are characterised by their unusual property of being easily soluble in dilute alcohol, some even being soluble in 96 per cent. alcohol. Ritthausen was the first to point out that the seeds of wheat, rye, barley, maize, and oats contain proteins which are insoluble in water and salt solution, but readily soluble in alcohol. In wheat these substances, together with the insoluble phyto-casein (glutenin), form the so-called gluten, the adhesive glue-like material, which is of the greatest importance in bread-making, by giving the necessary tenacity to dough. The chemical characteristics of this class are the high amount of glutaminic acid and the absence of glycine and lysine in their cleavage products. Only three substances of this class have so far been studied to any degree. They are called *wheat gliadin*, *zein* (from maize), and *hordein* (from barley).

Wheat Gliadin.—Ritthausen originally distinguished three alcohol-soluble substances in wheat which he called gliadin (plant glue), glutenfibrin, and mucedin. He was, however, unable to separate them quantitatively, and subsequent investigators, especially Osborne and Campbell, returned to the old view of Taddei's that there is only one alcohol-soluble substance, for which they retained the name of *gliadin*. It seems, however, preferable to call it wheat gliadin in distinction from the group name. It is identical with the substance obtained from rye, and amounts to 4 to 5 per cent. of the grain. It is insoluble in absolute alcohol, but easily soluble in 70 to 80 per cent. alcohol, and is precipitated from these solutions by the addition of water. It is especially characterised by the high percentage of glutaminic acid, which it furnishes on hydrolysis, amounting to 36 to 37 per cent., and the total absence of lysine among its cleavage products. On account of the strikingly different percentages of cleavage products from those of animal proteins, it was chosen by Abderhalden and Samuely for an interesting experiment with regard to the synthesis of proteins in the animal body. These observers found that on administering it to a horse which had previously lost a large amount of blood, the composition of the serum proteins remained constant.

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[1] Pick suggests a similarity to the proto-albumoses.

The alcohol-soluble protein of maize was called *zein* by Gorham, and subsequently maize-fibrin by Ritthausen. Osborne and Chittenden reinvestigated this substance and retained the name zein. It is characterised by its solubility in even strong alcohol of 96 per cent., and its complete insolubility in water. Glutaminic acid is also present in large quantities among its cleavage products, and lysine is absent. The indole-molecule (tryptophane) is also missing, and zein represents, therefore, a convenient material to investigate the question how far the absence of certain cleavage products influences the nutritive value of a protein. Hopkins and Willcock found that growth was very favourably influenced in young animals by zein and tryptophane, whilst zein itself was insufficient.

Hordein is the name given by Osborne to the alcohol-soluble protein of barley. Its differs somewhat from wheat gliadin in its solubilities, and contains more carbon and less sulphur than the latter. The hydrolytic cleavage products, examined by Osborne and Clapp, resemble quantitatively those of the other gliadins. Lysine is absent, and as much as 41 per cent. glutaminic acid was found. The most marked feature, however, is presented by the very large percentage of proline (pyrrolidine-carboxylic acid), which exceeds that yet obtained from any other protein, being practically 14 per cent., or twice as much as that yielded by wheat gliadin.

4. *The Phyto-caseins (or Phyto-vitellins).*—These substances are found in maize, barley, rye, and wheat, and amount in some cases to nearly 50 per cent. of the total protein. When these seeds are completely extracted by treatment with water, followed by salt solution and subsequently alcohol, the residue still contains a large amount of protein, which can only be extracted by treatment with very dilute (0·2 per cent.) alkali. From this solution they are precipitated by neutralisation with acids. They are insoluble in water and alcohol, but show both acid and basic properties, being easily soluble in a slight excess of alkali or acid. The question of their per-

centage of phosphorus has not yet been definitely settled. It may be mentioned here that, according to the unpublished results of an investigation carried out by Dr. Kajiura and the author on the proteins of rice, this cereal also contains a similar substance, which forms the bulk of the rice proteins. Curiously enough, although rice forms the staple food of Oriental races, its proteins have not until now been examined.

The best-known representative of this class is *glutenin*, the alcohol-insoluble part of gluten of wheat. This substance may be easily prepared by the method explained above. In distinction from its constant companion, the wheat gliadin, it furnishes only 9 per cent. glutaminic acid, and contains 2 per cent. lysine amongst its cleavage products. The main interest consists in its connection with gluten-formation. There is still some uncertainty about the process of gluten-formation and the conditions regulating it. The question is an important economic one, as it is intimately connected with the "strength" of flour—*i.e.* the property of wheat which makes it pre-eminently suitable for bread-making.[1] The stiff coherent mass which is formed when wheat-flour is mixed with cold water owes its formation to the presence of proteins, for no such action takes place when pure wheat-starch is mixed with cold water. The question arises whether the gluten proteins exist pre-formed in the grain, or whether they are produced by a secondary change. Weyl and Bischoff compared this process to fibrin formation from fibrinogen in the coagulation of blood, and they assumed the existence of a ferment which transforms in the presence of water the gluten-forming substances into gluten. They were, however, unable to demonstrate such a ferment, and the experiments of Osborne and Voorhees, although they do not exclude ferment action altogether, seem to prove that gluten is formed by the chemical or physical interaction of its two constituents—the gliadin and glutenin. Attempts have been made to explain the relative "strength" of flour from wheat and other cereals by the quantitative relationship of glutenin to gliadin. It seems, however, to be more likely to depend on the physical state of the gluten, which is, as already shown by Ritthausen and Osborne, dependent on the presence of mineral salts.

[1] See A. E. Humphries, SCIENCE PROGRESS, vol. ii. 1907, 175.

It might be mentioned finally that, amongst the vegetable proteins, albumose-like substances have also been met with, but their existence as such in seeds is doubtful. Small quantities of peptones have also been observed.

Typical nucleo-proteins occur in plants. The nucleic acid, isolated by Kossel from yeast, was the first substance of this type known. Osborne and Harris have lately isolated and investigated very thoroughly a nucleic acid from wheat embryos. It furnishes characteristic purine bases on hydrolysis.

(To be continued)

REVIEWS

Textbooks of Physical Chemistry: Stoichiometry. By SYDNEY YOUNG, D.SC., F.R.S. Also an "Introduction to the Study of Physical Chemistry," by Sir William Ramsay, K.C.B., F.R.S., Editor of the Series. [Pp. lxi. + 381.] London: Longmans, Green & Co. *7s. 6d.*

NEARLY four years have elapsed since the first of these textbooks was issued. In that first volume the hope was expressed that the others of the series would be ready for the press before the end of 1904. This hope has not been realised; but so long as slight delay secures excellence of workmanship, and so long as the contents of each volume are brought up to date, one is prepared to cease grumbling and give a hearty welcome to each belated arrival.

In the case of two of the previous volumes there was just ground for complaint of the excessive bulk and price; treatises on Spectroscopy and Stereochemistry extending to 500 or 600 pages are really quite beyond the limits of a textbook, and out of proportion to the scale of the earlier volumes of the series.

It is therefore gratifying to find that Professor Young, notwithstanding the fundamental and extensive character of his subject, has contrived to give an excellent presentation of it within a reasonable compass. In gauging the extent of the ground which he has to cover, it must be remembered that "stoichiometry" means a good deal more nowadays than it once did. Although not a very common word, it is more than a century since it was first used by Richter to denote the determination of the proportions in which substances combine. Subsequently the meaning has been extended to comprehend not only the determination of atomic and molecular weights, but also the study of the general properties of gases, liquids, and solids, the behaviour of mixtures, solubility, the properties of dilute solutions, and other kindred subjects.

On the relationship between the gaseous and the liquid states, and on cognate problems, Professor Young is especially qualified to write, in virtue of his own extensive and admirable investigations, but in the other parts of the book also the treatment is generally good. A critical perusal of the two chapters on the determination of atomic weights may be recommended, for much loose thinking on this subject is current even among advanced students.

As regards the division of the available space among the various sections of stoichiometry, and as regards the arrangement of the chapters, there is some room for criticism. Only twenty-four pages are allotted to the consideration of the properties of dilute solutions—a space which, in view of the part played by dilute solutions in the development of modern physical chemistry, is decidedly inadequate. When this small space is compared with the 130 pages devoted in a previous volume to the subject of steric hindrance it is obvious that the scale of treatment by the different authors of the textbooks has been very far from uniform.

The chapter on the properties of dilute solutions not only suffers from undue brevity; in one respect, at least, it has not been brought up to date. The last few years have witnessed a remarkable advance in our experimental knowledge of osmotic pressure—an advance chiefly due to Lord Berkeley and Mr. Hartley, on the one hand, and to Messrs. Morse and Frazer, on the other. The work of the latter investigators is of the utmost importance, involving an extension to concentrated solutions of van 't Hoff's formula for dilute solutions. In Professor Young's discussion of osmotic pressure, however, no reference is made to Morse and Frazer's work.

In regard also to the arrangement of the chapters a word of criticism may be permitted. To devise an arrangement which should be universally acceptable is perhaps a vain hope, but it does seem curious that a chapter on "The Dissociation of Gases and Vapours" should be placed between one on "The Periodic Law" and one on "The Properties of Liquids." The author may have a good reason for this arrangement, but it would seem more rational to discuss cases of abnormal vapour density in that portion of the book which deals with the molecular weights of gases and vapours. Again, the insertion of a discussion of the kinetic gas theory between chapters on the properties of liquids and the properties of solids is open to criticism. It is no doubt true that this theory is closely connected with van der Waals' equation of state, but it should be discussed primarily in relation to the experimental gaseous laws. The three gaseous laws which must be regarded as fundamental by the physical chemist are (1) Boyle's Law, (2) Gay Lussac's Law, (3) Gay Lussac's Law of Volumes, and the descriptive exposition of these should be followed immediately by a discussion of their theoretical basis in the kinetic gas theory and Avogadro's hypothesis.

But although there thus appears to be some ground for criticism, Professor Young's volume may be cordially commended to all those who seek to familiarise themselves with the point of view of physical chemistry—a point of view which is both rational and stimulating.

J. C. PHILIP.

Physiography. By ROLLIN D. SALISBURY, Professor of Geology and Head of the Department of Geography in the University of Chicago. London: John Murray. 1907.

IN this country the term physiography is applied by the Board of Education to an assemblage of theoretical and experimental material, gathered from nearly every branch of science, to form a subject for instruction and examination in our elementary schools. In the United States, on the other hand, it is employed with a more definite meaning and concerns itself with the physical aspects of our planet and their variations in time and space. It is a favourite study in the higher classes in schools, and lower classes in colleges, and the present volume is one of the best that has appeared in recent years to satisfy the demand for a textbook on the subject. Its most striking characteristic is its wealth in illustration. Every stage in the evolution of the land is depicted in clearly reproduced photographs of American scenery; the diagrams are striking, and in many cases original; but a still more important feature is the number of maps. These include effective photographs from models, graphic representations of the distribution of physical phenomena, and transcripts and facsimiles of the topographical maps of the United States Geological Survey. These last are closely contoured, and give an excellent idea of the form of the earth's surface. One is glad to be reminded by the author that the originals can be obtained from the Director of the Survey at Washington at the rate of three dollars a hundred, which works out at about three-halfpence each. The author is to be congratulated on the fact that he has in every case restricted his maps and diagrams within the limits of the format of the book, thus avoiding the inconvenience of folded sheets.

Though showing occasional traces of haste, the text is as a rule clear and readable, besides containing much that is suggestive and original. Perhaps the least satisfactory portion of the book is that which deals with the regional distribution of pressure in high latitudes, the explanations that are offered being hardly calculated to carry conviction to the mind of the student. It is true that much remains to be done in working out the details of the subject ; but the main principles admit of very simple expression. Briefly, the variations in pressure on the earth's surface are dependent on differences of temperature, moisture, and centrifugal force—to use a useful term by no means free from objection but sufficiently well understood. The tendency of heat alone would be to make the pressure increase continuously from the equator to the poles. That of centrifugal force alone has exactly the contrary effect, for air moving towards the poles has a greater rotational velocity than that proper to its new latitude, and therefore tends to rise, while air moving towards the equator tends to sink. The magnitude of this effect is dependent on the rate of change in the length of the radius of rotation, a rate which increases rapidly as the pole is approached. Thus it comes about that while the influence of heat difference is greater in low latitudes that of difference of centrifugal force is more powerful in high latitudes. If then the earth were a uniform solid spheroid, there would be a belt of low pressure round the equator and two areas of low pressure at the poles with high-pressure belts between. In the colder regions, however, the air over the open sea is as a rule warmer as well as moister than that over ice or land masses. Tracts of open sea in high latitudes are therefore characterised by abnormally low pressure. Accordingly we find in the North Atlantic and Pacific two areas of low pressure imposed upon the regular decrease of pressure from the horse latitudes to the North Pole itself. Similarly in the Southern Hemisphere the open circum-antarctic sea gives rise to a circle of abnormally low pressure. Beyond, in the region of Antarctic land and ice, the pressure is probably somewhat higher, representing the normal low pressure of the pole.

There are some minor points on which a word of explanation might have been added for the benefit of English readers. For instance, on page 509 we find the word "billion" used in the popular American sense of a thousand million instead of the square of a million, according to the usage of mathematicians, though, curiously enough, in a quotation from Sir John Herschell, on the very next page, a trillion is employed correctly, without comment, for the cube of a million. On page 613 we are told that the "English" unit of pressure gradient is a hundredth of an inch in seventeen miles, which appears a very unreasonable convention in the absence of the explanation that it is equivalent to one millimetre in a degree.

These however are minor matters. The book as a whole is excellent, and the best testimony to its value is the keen interest it has awakened in every student in whose hands it has been placed.

JOHN W. EVANS.

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